SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

MANIKANDAN.R

REGISTRATION No. 261511103

Under the Guidance of

Dr. S.SUBRAMANIAN, M. Pharm., Ph.D.,

Department of Pharmaceutics

PSG COLLEGE OF PHARMACY

PEELAMEDU

COIMBATORE 641 004

October 2017

CERTIFICATE

This is to certify that the dissertation entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** is a bonafide work submitted by **Reg. No. 261511103,** to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment for **Master of Pharmacy** in **Pharmaceutics** and has been conducted under the guidance of **Dr. S. SUBRAMANIAN M.Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Peelamedu, Coimbatore in the academic year of 2016-2017.

Guide:
Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,

Head of the Department:
Dr. V. Sankar M.Pharm, Ph.D.,

Principal:
Dr. M. RAMANATHAN, M. Pharm, Ph.D.,

Dr. M. RAMANATHAN, M. Pharm, Ph.D.,
Principal,
PSG College of Pharmacy,
Coimbatore - 641 004. (T.N)

CERTIFICATE

This is to certify that the dissertation work entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** submitted by **University Reg. No. 261511103** is a bonafide work carried out by the candidate under the guidance of **Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,** and submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics**, and has been conducted under the guidance of **Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017.

Place: Coimbatore
Date:

Dr. M. Ramanathan, M.Pharm, Ph.D.,
Principal

Dr. V. SANKAR, M.Pharm, Ph.D.,
Head of the Department,
PSG College of Pharmacy,
Coimbatore - 641 004. (T.N)

CERTIFICATE

This is to certify that the dissertation work entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** submitted by **University Reg. No. 261511103** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** and has been conducted under the guidance of **Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017

Place: Coimbatore **Dr. V. Sankar, M.Pharm, Ph.D.,**

Date: **Head of the Department**

Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,
Head of the Department,
PSG College of Pharmacy,
Coimbatore - 641 004. (T.N)

CERTIFICATE

This is to certify that the dissertation work entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** submitted by **University Reg. No. 261511103** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** and has been conducted under the guidance of **Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017

Place: Coimbatore **Dr. S. Subramanian, M.Pharm, Ph.D.,**

Date: **Associate Professor**

DECLARATION

I do hereby declare that the dissertation work entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics,** was done by me under the guidance of **Dr. S.SUBRAMANIAN M.Pharm, Ph.D.,** Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, during the academic year 2016-2017.

Reg. No. 261511103

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"SELF NANOEMULSIFYING TABLETS OF TELMISARTAN - DEVELOPMENT, CHARACTERIZATION, EFFECT ON DISSOLUTION"** submitted by **University Reg. No. 261511103** to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate at the Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore and was evaluated by us during the academic year 2016-2017.

Examination Center: PSG College of Pharmacy, Coimbatore.
Date:

Internal Examiner **External Examiner**

Convener of Examination

ACKNOWLEDGEMENT

Behind every achievement there are many helping hands, my work would be incomplete unless I mention the names of people those made it possible, whose constant guidance and encouragement served as a source of inspiration and energy made this success.

It is an honour to express my sincere thanks and gratitude to Head of the Department **Dr. V. Sankar, M.Pharm, Ph.D.,** Associate Professor for guiding me at every stage of the project and his absolute patience has inspired me a lot to venture towards the completion of my dissertation work.

It is an honour to express my sincere thanks and gratitude to my guide **Dr. S. Subramanian, M.Pharm, Ph.D.,** Associate Professor for guiding me at every stage of the project and his absolute patience has inspired me a lot to venture towards the completion of my dissertation work.

It is my privilege to acknowledge **Dr. M. Ramanathan, M.Pharm, Ph.D.,** principal, for providing the necessary facilities for carrying out this work.

Friends are treasures to me very time.it is very difficult to overstate my thanks to all my friends apparently **Jayakumar, Manivaasagam, Saravana bharath, Renuka Devi, Vijiyalakshmi, Senith.** It has been my happiest time to study with them all.

Also I would like to thank **PSG Institutions-management** for providing a nice environment for learning. I felt delighted to express my whole hearted gratitude to all those who gave their helping hands in completing my course and my project successfully.

CONTENTS

CHAPTER NO	CONTENTS	PAGE NO
1.	Introduction	1
2.	Literature Review	23
3.	Drug Profile	28
4.	Excipients Profile	31
5.	Objective	40
6.	Plan of Work	41
7.	Materials and Instruments	42
8.	Preformulation Studies	44
9.	Experimental Methodology	46
10.	Results and Discussions	54
11.	Summary and Conclusion	82
12.	Bibliography	83

LIST OF TABLES

TABLE NO	PARTICULARS	PAGE NO
1.	Components of SNEDDS	19
2.	Calibration curve of Telmisartan	45
3.	Composition of Telmisartan SNEDDS formulation	47
4.	Grades for the visual assessment of self nano emulsifying formulation	49
5.	IP limits for weight variation	51
6.	FT- IR data of Telmisartan	55
7.	FT- IR data of Pluronic F 127	56
8.	FT- IR data of microcrystalline cellulose	57
9.	FT- IR data of span 60	58
10.	FT- IR data of Drug+excipients	59
11.	Calibration curve of Telmisartan	60
12.	Solubility studies in oil	61
13.	Percentage transmittance of surfactants	63
14.	Visual assessment and self emulsification time of SNEDDS and S-SNEDDS Formulations	65
15.	Characterzation of S-SNEDDS formulations	66
16.	Micromeritics properties of SNE powder formulation (Before adding glidant)	72
17.	Micromeritics properties of SNE powder formulation (After adding Talc 2%)	72
18.	Compression of telmisartan SNE tablet	73
19.	Weight variation test	76
20.	Fraiability test	76

21.	Hardness test	77
22.	Disintegration test	77
23.	Dissolution data of FT11 telmisartan SNE tablet	78
24.	Dissolution data of FT12 Telmisartan SNE tablets	79
25.	Dissolution data of FT13 Telmisartan SNE tablet	80
26.	Dissolution data of Telmisartan tablet-marketed formlation	81

LIST OF FIGURES

FIGURE NO	PARTICULARS	PAGE NO
1.	Schematic representation of the various challenges to the oral delivery of drugs	2
2.	Biopharmaceutical drug classification system	2
3.	Strategies to improve the oral bioavailability of drug substances	4
4.	Types of Self emulsifying drug delivery system	12
5.	Self Emulsifying drug delivery system	14
6.	Preparation of SNEDDS	16
7.	Mechanism of action of Telmisartan	21
8.	Structure of Telmisartan	28
9.	Calibration curve for Telmisartan	45
10.	FT-IR data of Telmisartan	55
11.	FT-IR data of Pluronic F 127	56
12.	FT-IR data of microcrystaliine cellulose	57
13.	FT-IR data of Span 60	58
14.	FT-IR data of Drug+excipients	59
15.	Calibration curve for Telmisartan	60
16.	Solubility studies in oil	61
17.	Percentage transmittance of surfactants	63
18.	Pseudo Ternary phase diagram	64
19.	Particle size of FT11	67
20.	Particle size of FT 12	68
21.	Particle size of FT13	69
22.	SEM image of FT11	70

23.	SEM image of FT12	70
24.	SEM image of FT13	70
25.	FT11 Telmisartan SNE tablets	74
26.	FT12 Telmisartan SNE tablets	74
27.	FT13 telmisartan SNE tablets	74
28.	Formulation of Telmisartan Liquid SNEDDS	75
29.	Dissolution profile of FT11 SNE Telmisartan tablet	78
30.	Dissolution study of FT12 SNE Telmisartan tablets	79
31.	Dissolution profile of FT13 SNE Telmisartan tablets	80
32.	Dissolution profile of Telmisartan marketed tablets	81

LIST OF ABBREVATION

UV	- Ultra violet
FT-IR	- Fourier Transform Infrared
PEG 400	- Polyethylene glycol 400
PG	- Propylene glycol
SNEDDS	- Self nanoemulsifying drug delivery system
SNET	- Self nanoemulsifying Therapeutic system
SEDDS	- Self emulsifying drug delivery system
SEM	- Scanning electron microscopy
PDI	- Poly dispersive index

INTRODUCTION

Around fourty percent of new chemical entities developed by the pharmaceutical industry are poorly soluble or lipophilic compounds, which result poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality.

Oral delivery route is the most convenient route for drug administration to achieve desired therapeutic effects and the greatest degree of patient compliance, especially for chronic condition diseases. Despite some clinical oral formulations have been developed, their low oral bioavailability is still a major hurdle, leading to challenges for pharmaceutical manufacturers to design delivery systems that can provide improved pharmacokinetic profiles and therapeutic responses. Currently, many efforts such as efflux pump inhibitors, permeation enhancers and drug nanonization, have been made to overcome the challenges of low oral bioavailability resulting from low drug solubility, poor permeation and enzymatic degradation, which limiting drug effective delivery.

Advantages of oral delivery systems

Oral administration is the most widely accepted and preferred route for pharmaceuticals, due to its high convenience and better patient compliance. Oral administration of drugs can avoid hospitalization, sterile manufacturing and trained personnel assistance, so reducing the cost of the health treatment. Pharmaco-economic analyses were performed in clinical trials to evaluate the economic effectiveness of various oral drugs and to make a contrast with the cost of infusion administration.

Challenges in the oral drug delivery

Regardless of many advantages, the development of oral delivery route still represents a great challenge owing to peculiar physicochemical properties of lipophilic drug candidates, and physiological barriers such as gastrointestinal instability, pre-systemic metabolism and efflux pump. Upon oral administration, lipophilic drug in a dosage form is easily ingested by patients, travels in the GIT passing through an extremely various environment. When drug transits from a strong acidic pH in stomach to basic environment of the intestine, it encounters harsh pH changes, but also different digestive enzymes and the resident micro flora.

After the digestive journey, only a fraction of dose is available to systemic circulation for the execution of therapeutic response. In view of this, the principal challenges to the oral delivery

are classified into physicochemical properties of drugs and physiological barriers posed by human body (Figure 1).

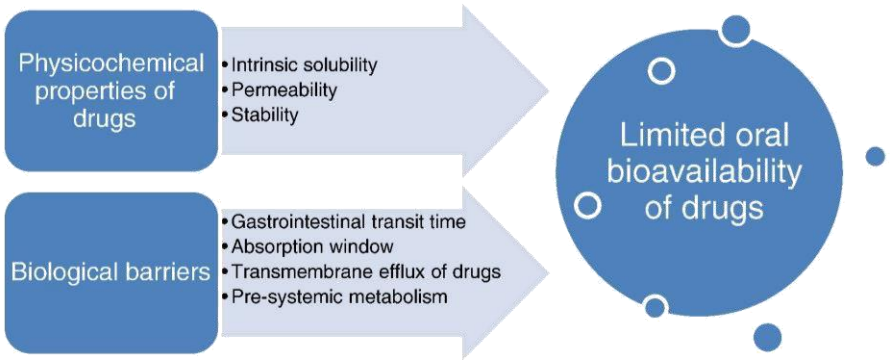


Figure 1: Schematic representation of the various challenges to the oral delivery of drugs.

Biopharmaceutical drug classification system

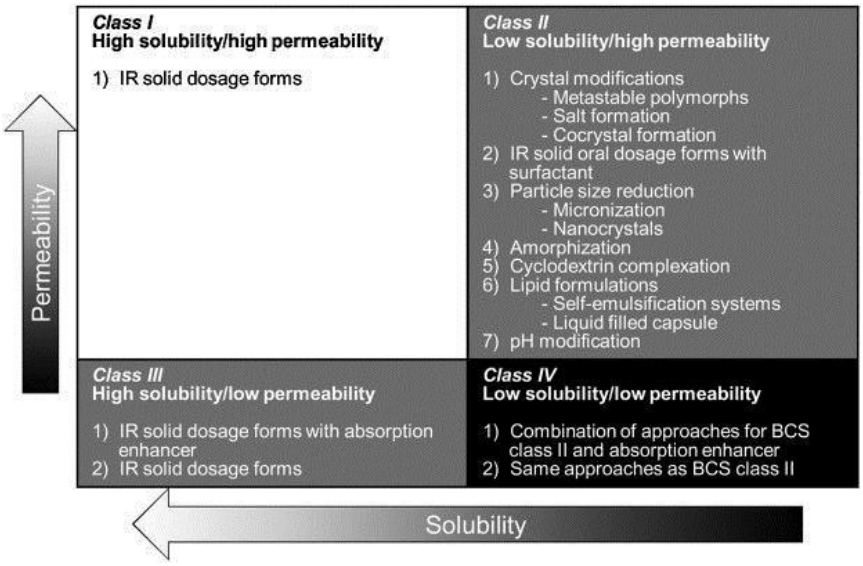


Figure 2: Biopharmaceutical drug classification system

Class I includes drugs that are water soluble and gastrointestinal tract permeable. This class does not suffer from absorption or permeation problems that may affect oral drug bioavailability. While classes II, III and IV contain drugs having problems in solubility and/or Permeability that may reflect on their bioavailability in the blood after the drug is taken orally. Classes II, III and IV form approximately 80% of the drugs available in the market.

Solubility of drug substances

A plenty of organic materials are poorly soluble in water. The poorly water-soluble drugs are typical examples. Poor solubility of a drug is in most cases associated with poor bioavailability. Furthermore, in drug discovery, about 40% of new drug candidates display poor solubility in water, which leads to low bioavailability, erratic absorption, high intra-subject and inter-subject variability and lack of dose proportionality. From a physicochemical point of view, poor aqueous solubility and low dissolution rate are the major factors that affect oral delivery of many existing lipophilic drugs. Improving the drug solubility might only solve one aspect of the problem but it is a starting point to design efficient pharmaceutical formulations.

Gastrointestinal transit

Human digestive system is complicatedly designed to safely, selectively, and effectively absorb as many nutrients as possible from our diet. In the case of drug delivery, after the oral administration, drug candidates have to reach final absorption site – intestine. However, the gastrointestinal tract (GIT) presents various chemical and enzymatic barriers that affect delivery of drugs. During the drug transit, the pH of the GI tract lumen rises from the strongly acidic (pH 1.0–2.0) in the stomach, to 5.0–6.0 in the duodenum, to basic (pH 7.0-9.0) in the jejunum. On the other hand, variety of enzymes that include lipases and proteases also function to initiate foodstuff digestion and destroy unwanted pathogens and toxins. Furthermore, the gastrointestinal transit time is another factor that significantly affects oral bioavailability and efficacy of many drugs.

Many efforts have been done to enhance the duration for absorption, like the dosage form mucoadhesive. The use of mucoadhesives can increase local drug concentrations for absorption enhancement, improve the efficiency for prolonging drug resistance time, and in some cases restrict absorption to a specific site in the intestine. So far, various types of approaches have been successfully developed to extend the gastrointestinal transit time, further to improve the intestinal permeability and to enhance the oral bioavailability.

Approaches for enhancement of oral bioavailability

The common approaches to improve the systemic bioavailability of drugs are to deliver them by alternative administration routes such as oral, transdermal, nasal, vaginal or rectal.

Among these routes, oral administration is the most convenient way to achieve the desired therapeutic effects.

Numerous pharmaceutical scientists have logically focused on oral administration route to effectively enhance the bioavailability of the drug substances. The key approaches to maximize oral drug absorption are described as follows:

- By using efflux pump inhibitors to improve the efficiency of drug transport;
- By using permeation enhancers to inhibit drug degradation and improve permeability;
- Modifying the physicochemical properties of drugs for improving drug solubility, stability and dissolution rate;
- Designing the specialized formulation such as nanoparticles, micro-particles and liposomes that improve the drug solubility and protect drugs from harsh environment of the gastrointestinal tract;
- Developing stimuli-responsive systems for controlled drug delivery summarizes the various strategies that have been investigated and proposed to improve the oral bioavailability of drug substances.

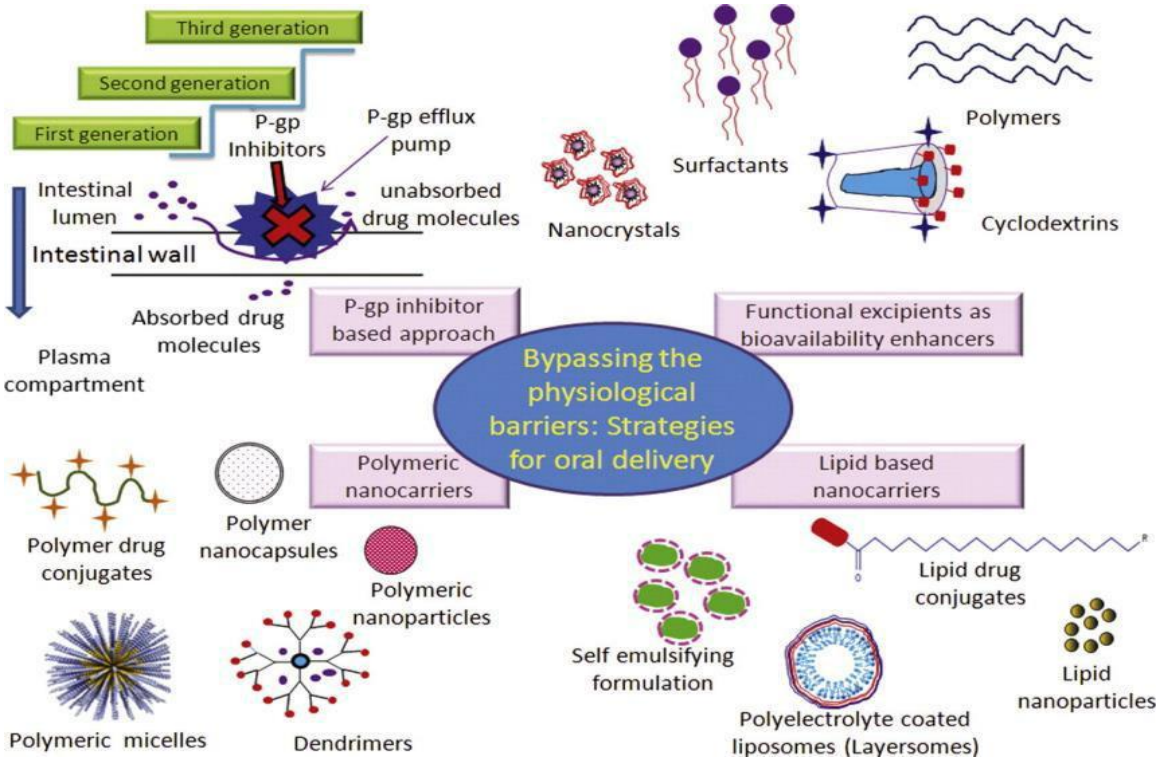


Figure 3: Strategies to improve the oral bioavailability of drug substances

LIPID BASED DRUG DELIVERY SYSTEMS

Drugs which are poorly water solubility are made well suitable for lipid-based formulation. Water insoluble and weakly basic drugs require special care in the design and development of lipid based formulation. These drugs administered in the solubilized form in the lipid vehicle may come out of the formulation due to solubilisation in the gastric fluid and may precipitate in the intestinal fluid on gastric emptying. The bioavailability of this system would depend on how rapidly the precipitates can be resolubilized by the formulation.

The percentage of new chemical entities synthesized with low aqueous solubility and high therapeutic efficacy is growing, this presents a major challenge for the drug delivery. To overcome the above challenge different methods were developed for the enhancement of bioavailability.

Lipid based formulations are more effective delivery system for oral route and improve bioavailability because of its proven safety and efficacy. Lipid Formulation Classification System was established by Pouton et al., It aims to enable *in vivo* studies for interpreting and for the identification of the most appropriate formulations for specific drugs, their physiochemical properties are taken into consideration.

Lipid-drug conjugates

To overcome the limitation of limited loading capacity for highly potent hydrophilic drugs and drug expulsion during storage, lipid-drug conjugates have been made. Lipid-drug conjugates nanoparticle are prepared either by formation of a salt with a fatty acid or alternatively by covalent linkage (e.g. to ester or ethers). Further process is perform an aqueous surfactant solution to a nanoparticle formulation using high pressure homogenization. The lipids that can be used for formulation of lipid–drug conjugates include phospholipids, fatty acids such as stearic acid, oleic acid, docosahexaenoic acid, etc. and lipoamino acids.

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are composed of melt-emulsified solid lipids like highly purified triglycerides, monoglycerides, hard fats, complex glyceride mixtures as matrix materials. As they are derived from biodegradable and compatible lipids, SLN represents a comparatively stable system with protective effects against serious drug toxicity and harsh external environment in comparison to the conventional nanoparticles. In addition, they also

offer the advantages of avoidance of organic solvents in their preparation, controlled release of drugs and excellent tolerability.

Of the available methods for preparation, cold high-pressure homogenisation process, hot homogenization of melted lipids at elevated temperatures and microemulsion technology are considered as the most feasible methods for large scale production of SLNs. Although solid lipid nanoparticles (SLNs) have attracted increasing attention due to its advantages, SLNs have several limitations, for example, low loading efficiency for some drugs which owing to the densely packed lipid crystal network. Furthermore, SLNs also show considerable expulsion of the drug during storage.

Lipid nanocapsules (LNCs)

Lipid nanocapsules (LNCs) provide a new nanotechnology which contributes to oral drug delivery development. LNCs are another kind of lipid nanoparticles, composed of an internal liquid or semi-liquid oil core and an external lipid layer solid as a core-shell structure. LNCs with the unique properties such as controlled release profiles and high bioavailability, represent a promising biocompatible drug delivery platform in nanometer range with narrow size distribution. The phase inversion temperature (PIT) method proposed by Shinoda and Saito led to lipid nanocapsules preparation with good mono-dispersion. LNCs prepared by PIT method is based on three main components: an oil phase, an aqueous phase and a non-ionic surfactant.

Furthermore, the temperature cycling process crossing the phase-inversion zone (PIZ) plays another role on LNCs formulation. Increasing the number of cycles promotes LNC formation and improves the quality of LNC dispersion. Recently, many lipophilic drugs have been developed in LNCs form for instance, ibuprofen loaded LNCs for pain treatment; indinavir, an inhibitor of HIV1 protease; various hydrophobic anticancer agents. Consequently, LNCs provide an attractive drug delivery approach for highly lipophilicity drug substances that are usually unsuitable for oral use.

Nanosuspensions

Nanosuspensions are nanoscale colloidal dispersion of solid drug particles which are stabilized by surfactants, polymers or a combination of both. The key difference from conventional suspensions is that the particle size distribution of the solid particles in nanosuspensions is usually < 1 µm. Nanosuspensions engineering processes presently used are

media milling, high pressure homogenization, microprecipitation-high pressure homogenization, emulsion diffusion method and melt emulsification method. Owing to the enhanced drug solubility, increased surface-volume ratio of the nanocrystals, and improved dissolution rate, oral nanosuspensions have been specifically used. Furthermore, nanosuspensions are available in various dosage formats such as tablets, pellets, and capsules following different manufacturing techniques. Nevertheless, the major challenges in nanosuspensions preparation are maintaining colloidal stability and particle size of the nanosuspensions during storage. The appropriate selection of the surfactants and/or steric stabilizers and the method of fabrication have been sought to prevent the nanocrystal aggregation to achieve the nanosuspensions with long-term storage and physiological stability.

Liposomes

Liposomes are a form of self-assembled lipid bilayer vesicles which composed of one or more aqueous compartments are completely enclosed by hydrophilic and/or hydrophobic molecules. Due to the core (aqueous)-shell (lipidic) structure, liposomes are available for encapsulating hydrophilic drugs in the aqueous core, hydrophobic agents in the lipidic shell, meanwhile, amphiphilic molecules distributed through the hydrophobic-hydrophilic layers. In addition, using biologically and natural lipids makes liposomes highly biocompatible and suitable for in vivo use.

Recently, research on liposomes technology has been extensively investigated for the delivery of various therapeutic and bioactive agents, decreasing toxicity and increasing their accumulation at target sites. Nitesh Kumar *et al* developed lecithin-based silymarin liposomes. The results showed that incorporating phytosomal form of silymarin in liposomes had better *in vitro* and in vivo hepatoprotection and better anti-inflammatory effects in histopathological changes. Therefore, liposomes can be used in the oral delivery of lipophilic drugs to increase its oral bioavailability.

Liquid crystalline nanoparticles (LCNPs)

Liquid crystalline nanoparticles (LCNPs), which combine the properties of both liquid and solid states, are self-assembled from polar amphiphilic lipids in the presence of excess water. LCNPs are generally prepared by dispersing the liquid crystalline matrix formed into water phase using high-energy fragmentation, such as ultrasonication, microfluidization, or homogenization. Normally, LCNPs enhance the oral bioavailability of lipophilic drug by

improvement of bioadhesiveness, membrane fusing properties, superior encapsulation, solubilization, etc. Ni Zeng *et al* developed self-assembled LCNPs consisting of soy phosphatidylcholine and glycerol dioleate for oral delivery of paclitaxel. The results of this study suggest that LCNPs could be a promising approach for enhancing the oral bioavailability of lipophilic drugs and agents.

Self-Nanoemulsifying drug delivery system (SNEDDS)

Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that rapidly form fine oil-in-water (o/w) nanoemulsions when introduced into aqueous medium under mild agitation. In the human body, the agitation required for formation of nanoemulsions is provided by digestive motility of the gastrointestinal tract. In comparison with the ready to use nanoemulsions or nanosuspensions, SNEDDS have shown many advantages such as: physical or chemical stability profile improvement in long term storage; possibility of filling into soft/hard gelatin capsules, which results in attractive commercial viability and patient acceptability; no palatability-related issues.In recent years, Self-emulsifying drug delivery systems (SNEDDS) is used to improve the oral bioavailability of poorly water-soluble drugs.

Polymer based nanocarriers

Polymeric nanoparticles

Polymeric nanoparticles are submicronic solid particles where drug is encapsulated or adsorbed onto particles. With the increasing study on polymers, polymeric nanoparticles have emerged as a promising approach in oral drug delivery field due to their unique properties such as improved drug stability, the duration of the therapeutic effect and to minimize drug degradation and metabolism etc. A variety of biodegradable and biocompatible polymers have been used in the research of polymeric nanoparticle preparation include starch, chitosan, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), etc. These polymers can be used either separately or combined with each other. The advantages of polymeric nanoparticles can be their high stability in the gastrointestinal tract, protection and controlled release of the incorporated drugs, flexibly modulating, and offering targeting with improved cellular uptake. However, the potential challenge for polymeric nanoparticles is associated with the polymer toxicity and the residues of organic solvents during the preparation. In addition, some of the synthetic polymers are highly hydrophobic and not

friendly to hydrophilic drugs. These limitations of polymeric nanoparticles should be addressed in the future studies.

Polymeric micelles

Polymeric micelles are nanosized supramolecular constructs formed by amphiphilic molecules consisting of an inner hydrophobic core and an outer hydrophilic entity. As a core-shell structure, the hydrophobic core acts a reservoir for lipophilic drugs whereas the hydrophilic shell protects the drugs to avoid the inactivation and increase the bioavailability and retention.

Two main methods have been commonly used to produce drug-loaded polymeric micelles. Direct dissolution involves dissolving both polymer and drug in an aqueous solvent. Alternatively, organic solvents are employed when both polymer and drugs are highly hydrophobic. As reported by literatures, polymeric micelles are stable in terms of both thermodynamic and kinetics, imparting overall structural stability. Moreover, polymeric micelles allow a multifunctional design to achieve integrated diagnostic and therapeutic functions and molecular targeting capabilities. Nevertheless, more efforts are still required in order to overcome the challenges, for examples, low drug loading, low permeability in transport through intestinal membrane.

Polymer-drug conjugates

By definition, polymer-drug conjugates are formed by the conjugation of a biocompatible polymeric carrier and low-molecular weight biologically active molecule(s) through a biodegradable linker. One of the major differences between polymer–drug conjugates and other nanocarriers that contain physically entrapped drugs is that the drug molecules are covalently bound to the polymers. Mostly, the presence of polymers increases the solubility of hydrophobic drugs, modifies drug dispersion profile, extends plasma circulation half-life, and improves its pharmacokinetic profile, in turn, enhancing the oral bioavailability of the drugs. On the other hand, the biodegradable linker can also become active by triggering drug release under certain conditions, such as a change in pH or in the presence of enzymes, such as esterases, lipases or proteases. A pH-sensitive amphiphilic dendritic polyrotaxane drug-polymer conjugate by covalently linked doxorubicin (DOX) and dendritic polyrotaxane has been designed and successfully fabricated by Yang Kang *et al.* This pH-sensitive drug-polymer conjugate showed a significantly faster drug release at mildly acidic

condition while without burst release in aqueous at a physiological pH of 7.4. The results proved that this conjugate has tremendous potentials for targeted cancer therapy.

Drug nanocrystals

Besides liposomes, nanocrystals are the most successful nanocarriers when considering the first marketed products as well as the total number of commercial products and in clinical phases. Nanocrystals are nanosized crystals of pure drug particles with the surfactants or polymeric steric stabiliser absorbed onto the surface of drugs. Thus, drug nanocrystals possess a 100% drug loading in contrast to polymer or lipid-based nanoparticles. As we known, decrease in particle size provides a greater surface area in the diffusion layer and leads increase of the drug dissolution rate, furthermore, enhancing the absorption . Industrially, the drug nanocrystals are produced with four main technologies, including top-down (e.g. pearl milling, high pressure homogenisation), bottom-up (e.g. precipitation) and combination (sonication–precipitation) and chemical approaches.

Dendrimers

Dendrimers are the new artificial well-defined polymeric nanostructures exhibiting tree-like architecture that consist of a hydrophobic central core, branching units and terminal functional groups. Dendrimers possess definite molecular weight, shape, size and specific physicochemical properties including host–guest entrapment properties. Unlike many traditional polymeric nanocarriers, dendrimers can be manufactured in almost any size whereas the diameters are commonly 10-20 nm. In addition, dendrimers also have a narrow polydispersity and well defined spherical shape with a variety of terminal functional groups. These unique structural nanosized macromolecules offer multiple ways for incorporation of plenty of drugs which pose oral delivery challenges.

First, drug molecules can be physically encapsulated in the core of the dendrimers. Second, drug molecules can be chemically conjugated to the functional end groups on the dendrimer surface during or after synthesis. Third, dendrimer drug networks can be formed. As an approach for the oral bioavailability enhancement, dendrimers provide many potential mechanisms. First, the dendrimers entrap the drugs to prevent the drug degradation from harsh gastrointestinal tract. Next, dendrimers may act as permeability enhancers and alter the barrier of the intestinal epithelium, thereby improve the drug absorption. Last, the dendrimer-drug conjugate may be transported across the intestinal epithelium by itself. The properties of

dendrimers such as size, surface charge and conformation significantly affect the drug delivery and absorption in the GIT. Moreover, larger dendrimers have been found be more toxic, in comparison with the smaller ones. Conclusively, dendrimers are promising delivery system, but more efforts should be required to overcome challenging biological barriers.

Others

Except the above mentioned strategies, many other nanotechnologies are also employed in the oral drug delivery, for example, carbon nanotubes, silica and silicon nanoparticles, nanogels and so on. Carbon nanotubes possess unique hollow cylindrical structures, high surface area, conductivity, optical and potential higher absorption capabilities, allow the incorporation of drug molecules for controlled and site-specific delivery. Silica/silicon nanoparticles offer a high absorption capacity, mesoporous channel to change the crystalline state of the drugs and the possibility to tailor the physicochemical properties. The biocompatibility, chemical properties and mesoporous structure make silica/silicon nanoparticles an excellent alternative for drug delivery application. Nanogels are commonly used for oral controlled drug delivery with the advantages such as thermodynamic compatibility with water, enviro-intelligent, stimuli-sensitive and sustained release.

In recent years, SNEDDS have attracted more and more attention as the mean to enhance the oral bioavailability of poorly soluble and highly metabolized drugs. Nevertheless, conventional SNEDDS also require a relatively large amount of surfactants, which may induce GI irritation and side-effects. In order to achieve a safe and efficient delivery system for the poor oral bioavailability drugs, we have designed a novel self-nanoemulsifying drug delivery system with high proportion lemon essential oil as carrier for lipophilic drugs.

Self-emulsifying drug delivery systems (SEDDS)

Self-emulsifying drug delivery systems (SEDDS) are emulsion pre-concentrates or anhydrous forms of emulsion. These systems (SEDDS) are ideally isotropic mixtures of drugs, oils and surfactants, sometimes containing co-surfactant or co-solvents. Upon mild agitation followed by dilution with aqueous media, SEDDS can form fine oil-in-water emulsions spontaneously. In gastrointestinal tract of human body, the agitation required for formation of emulsions is provided by gastric mobility, the aqueous media are gastrointestinal fluids. In comparison with ready-to-use emulsions, which are metastable dispersed forms, SEDDS possess improved physical and/or chemical stability profile upon long-term storage, and also

easy manufacture property. Thus, for the lipophilic drugs that exhibit poor water solubility and rate−limited dissolution, SEDDS may offer an improvement in the rate and extent of absorption and result in more reproducible blood−time profiles.

Types of SEDDS

SEDDS include both self-microemulsifying drug delivery systems (SMEDDS) and self-nanoemulsifying drug delivery systems (SNEDDS).

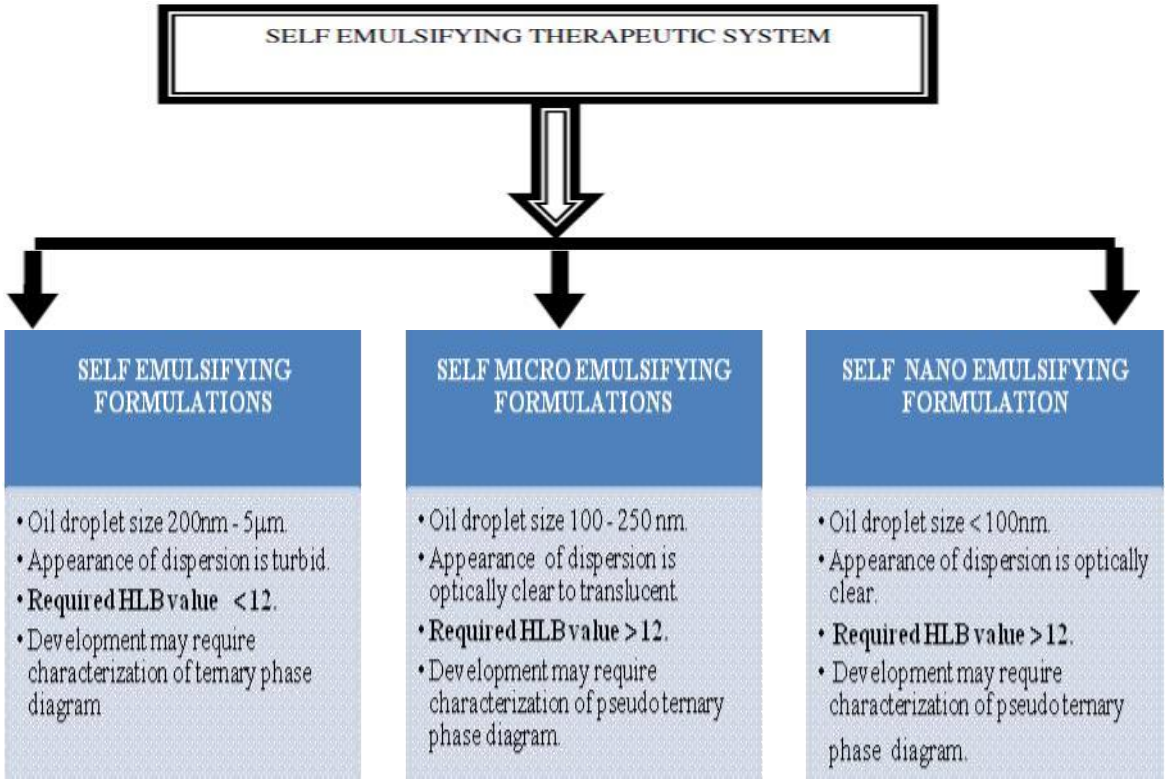


Figure 4: Types of Self emulsifying drug delivery system

SMEDDS indicate the formulations producing transparent microemulsions with droplets size range between 100 and 250 nm while SNEDDS form emulsions with the globule size range lower than 100 nm. The term ‘droplet’ is used to describe micelles, mixed micelles which exist in the emulsions. In details, the microemulsion is a thermodynamically stable colloidal dispersion consisting of small spheroid particles (comprised of oil, surfactant, and possibly co-surfactant) dispersed within an aqueous medium and thus in equilibrium. In contrast, the nanoemulsion is non-equilibrium colloidal dispersion system that over time spontaneously will exhibit coalescence of the dispersed droplets.

However, nanoemulsions can have a relatively high kinetic stability, and in this case it will be difficult to distinguish on the previous basis micro and nano-emulsions. Actually, the structure of the droplet in both nanoemulsion and microemulsion are very similar: the non-polar tails of surfactant molecules protrude into the lipophilic core formed by the oil, while the polar head groups protrude into the surrounding aqueous phase

Nanoemulsions

Nano-emulsions are a new class of emulsion which can be defined as an emulsion with uniform and extremely small droplet sizes, typically in the range of 20–200 nm. The physical appearance of nano-emulsion is transparent or translucent because of their small droplets size. Their small droplets size makes it kinetically stable against sedimentation or creaming for a long period of time. The use of nano-emulsions in oral dosage forms, achieve promising results in increasing the effectiveness of the drug at the target site, as well as can increase drug bioavailability, enhanced permeability and therapeutic functions. Efforts are madewith SNEDDS to enhance the oral bioavailability of lipophilic drugs in order to increase their pharmacological efficacy.

Nanoemulsions are non-equilibrium, heterogeneous systems composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. In a nanoemulsion, the oil droplets serve as the reservoir for hydrophobic drugs. Moreover, nanoemulsions are regarded as kinetically stable, isotropic and transparent without any apparent coalescence during the long time storage.

The nanoemulsions are usually stabilized by large amount of surfactants, which can improve drug solubilisation, protect active compound against physicochemical and enzymatic degradation and modify the permeability of the GIT membrane. Non-ionic surfactants are commonly preferred due to their less toxicity, less affected by pH and ions than ionic and amphiphilic surfactants, and better compatibility with biological systems. Combinations of different surfactants have also been employed to decrease the droplet size and improve the stability of nanoemulsions. Methods used for the production of nanoemulsions include high-pressure homogenization, microfluidization, ultrasonication, spontaneous emulsification and so on. The advantages of nanoemulsions are increased drug loading, tissue targeting and enhanced permeability.

SELF NANO EMULSIFIED DELIVERY SYSTEMS

Lipid based formulations such as self nano emulsified delivery systems (SNEDDS) are said to increase the absorption of the lipophilic drugs. SNEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug that form oil in water emulsion in aqueous environment under gentle agitation. This forms a good mode for delivering poorly soluble drugs orally by increasing their bioavailability and stability. They offer large interfacial area between the oil and GIT fluids and enhance the rate of absorption of the drugs

Self-nanoemulsifying Drug Delivery system (SNEDDS) is isotropic mixture of natural or synthetic oil, surfactants and co-surfactants that havea unique ability of forming fine oil-in-water (O/W) nano-emulsions under mild Agitation followedaqueous media. Self-Nano emulsifying Drug Delivery System having size range of globules is less than 100nm under dispersion of water.

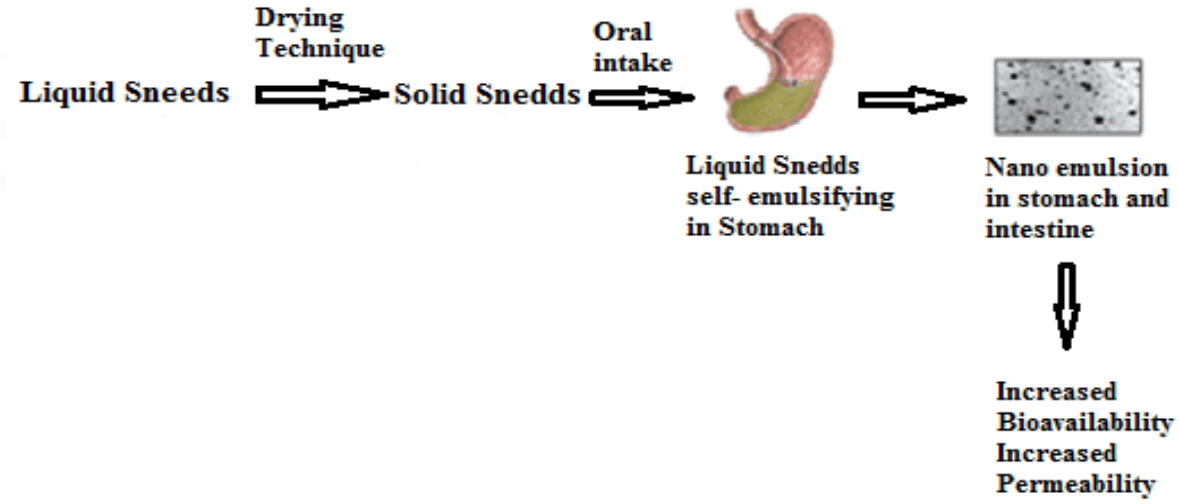


Figure 5: Self Emulsifing drug delivery system

SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. Spontaneous emulsification to produce fine oil-in-water emulsion under gentle agitation followed by dilution in aqueous media can occur in oil and surfactants mixture. The production of self-emulsifying formulation involves several combinations of oil and surfactants, also the efficiency of self-emulsifying formulation can be influenced by several factors such as HLB value of the surfactant and surfactant concentration. The components used must be suitable for oral ingestion, such as medium chain triglyceride oils and nonionic surfactants.

These SNEDDS are given in the form of soft or hard gelatin capsules or in the form of Tablets. They reach the gastro intestinal tract and the GI motility of the stomach provides the agitation for self-emulsification. Because of this self-emulsification the drug is given as small droplets with size less than 5μm for improved solubility. After administering orally, lingual and pancreatic lipases act on the oily phase of the SNEDDS that result in the formation of emulsified mono-glycerides, di-glycerides and fatty acids. This in the presence of bile acids leads to the formation of intestinal mixed micelles. When these mixed micelles pass through the enterocytes, it leads to the formation of chylomicrons. These drain the drug into the lymphatic vessels and not in the blood vessels thus bypassing the first pass effect. Thus the oral bioavailability gets increased.

These study shows preparation of various kind of SNEDDS formulation by performing trial batches of various oils (sunflower oil, soyabean oil, olive oil), surfactants (Acrysol derivatives and other Gattefosse surfactants, Tween 80, Tween 20), cosurfactants (captex 200,captex 300,labrafil M 2125) and cosolvents (PEG 400,Propylene Glycol, ethanol) with drug to assess the ability of drug in solubilized form and to form a transparent solution for better emulsification ratio of Surfactant: Cosurfactant: Cosolvents remains same. Nonionic surfactants with high HLB (HLB = 10) and subsequent hydrophilicity is necessary for the instant creation of oil in water droplets and/or rapid spreading of the formulation in the aqueous environment providing a good dispersing/self-emulsifying performance. The surfactants are amphiphilic in nature have ability to dissolve and solubilize to some extent high quantities of the hydrophobic drug. In SNEDDS generally surfactant of HLB value 8-16 is used.

Self nanoemulsifying drug delivery system (SNEDDS) has received particular attention as a means of improvement of oral bioavailability poorly soluble and absorbed drugs. SEDDS are the mixture of oils, surfactants, and co-surfactants. This becomes emulsify when come in contact with aqueous solution of GIT under the condition of gentle stirring and digestive motility. SNEDDS includes various dosage forms like capsule, tablets, beads, microspheres, nanospheres, etc. thus SNEDDS could efficiently improve oral absorption of the sparingly soluble drugs by self-emulsification. For the improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations.

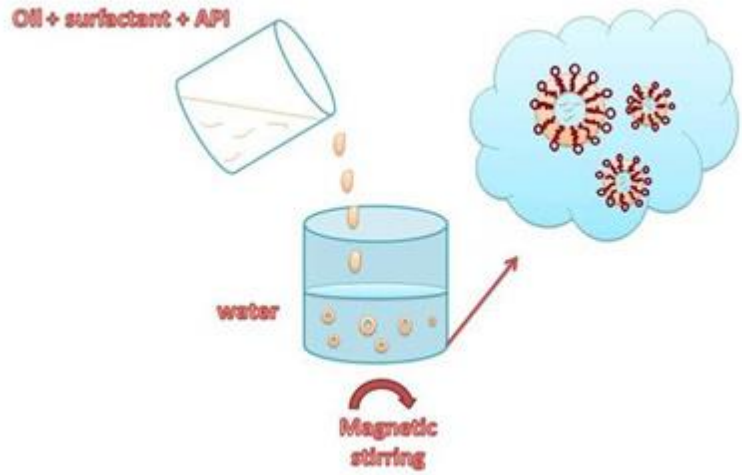


Figure 6: Preparation of SNEDDS

The bioavailability enhancing property has been associated with a number of *in-vivo* properties of lipidic formulation including:

- The formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
- The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favor improved drug absorption.
- The inhibition of cellular efflux mechanisms and pre-absorptive metabolism by gut membrane-bound cytochrome enzymes, further augmenting the absorption enhancing properties of these formulations.
- Certain lipidic excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.

SNEDDS are particularly useful when the poorly water soluble compounds are to be pre-dissolved in a suitable solvent and filled into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem with this system is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). But alternatively, if the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favor the drug remaining in the lipid droplets.

Some of the potential advantages of self-emulsifying lipid formulations include physicochemical stability, enhanced oral bioavailability enabling reduction in dose, consistent temporal profiles of drug absorption, selective targeting of drug towards specific absorption window in GIT, control of drug delivery profiles, ability to increase Cmax, AUC, and reduced tmax, linear AUC-dose relationship, reduced variability including effect of food, protection of sensitive drug substances, high drug payloads and flexibility of designing liquid or solid dosage forms.

Advantage of SNEDDS

1. Enhanced oral bioavailability enabling reduction in dose.
2. Selective targeting of drugs toward specific absorption window in GIT.
3. High drug payloads.
4. Control of delivery profiles.
5. Emulsion is sensitive and metastable dispersed forms while S(M)EDDS are physically stable formulation that are easy to manufacture.
6. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water.
7. SEDDS help to wide distribution of the drug throughout the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
   Potential advantages of these systems include enhanced oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut. Thus for lipophillic drug compounds that exhibit dissolution rate limited absorption, these system may offer an improvement in the rate and extent of absorption.

Disadvantages of SNEDDS

1. Traditional dissolution methods do not work, because these formulations potencially are dependent on digestion prior to release of the drug.
2. This in vitro models needs further development and validation before its strength can be evaluated.

Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.

The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

Limitation of SNEDDS

conventional SEDDS, which are mostly prepared in a liquid form and orally administered in soft or hard gelatin capsules, can make some disadvantages such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then incorporation of liquid SEDDS into a solid dosage form is compelling and desirable. Recentl y, a new drug delivery technology-solid SEDDS (S-SEDDS) which combine the advantages of SEDDS and those of solid dosage forms, have been investigated.

Factors affecting SNEDDS

Drugs which are administered at very high dose are notsuitable for SNEDDS, unless they exhibit extremely good solubility in at least one of the components of SNEDDS, preferably lipophillic phase. The drugs exhibit limited solubility in water and lipids are most difficult to deliver by SNEDDS.

The ability of SNEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent for drug solubilization, then there could be a risk of precipitation, as dilution of SNEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant.

Components of SNEDDS

It is very important to select and optimize the quantities of the SNEDDS components. Because the components of SNEDDS and their concentrations will influence the various characteristics of nano emulsions, such as droplet size, polydispersity index, self-nano emulsification time and *in vitro* drug release. In general, the selection of the components based on their ability to solubilize the drug of interest and also on their ability to form spontaneous emulsions/nanoemulsions. The various components of SNEDDS used in the table no.

Oils: Long and medium-chain triglyceride oils with different degrees of saturation have been used for the design of SEDDS. Oil can facilitate self-emulsification and increase the fraction of lipophilic drug transportation via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain 12-14 triglyceride.

Surfactant: Non-ionic surfactants are used in formulation of SNEDDSs. The usual surfactant concentration is between the ranges of 30–60% w/w of the formulation in order to form a stable SNEDDS. Surfactant having a high hydrophilic lipophilic balance (HLB) and hydrophilicity assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen.

Co-solvents: Co-solvents used in SEDDS helps to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base.

Table 1: Components of SNEDDS

Component	**Examples**	
	Fatty acids	Palmitic acid, Stearic acid, Oleic acid
	Fatty acid esters	Glyceryl monooleate [Capmul1 GMO,Imwitor1 948, Peceol1], Glyceryl monostearate [Capmul1 GMS-50, Imwitor1 191], Glyceryl monolinoleate [MaisineTM 35-1], Glyceryl palmito stearate [Precirol1 ATO 5], Glyceryl behenate [Compritol1 888 ATO] , Ascorbyl palmitate, Medium chain

		mono- and diglycerides [Capmul1 MCM], Medium chain triglycerides [Labrafac1 CC Miglyol1 810 and 812], Glyceryl dilaurate, Propyleneglycol monolaurate [Lauroglycol1 FCC, Capmul1 PG-12]
	Propyleneglycol esters	Propyleneglycol monolcaprylate [Capryol1 90, Capmul1 PG-8], Propylene glycol dicaprylocaprate [Labrafac1 PG]
	Miscellaneous	Stearyl alcohol,Phospholipids, Bees Wax,Vitamin E
Lipids and oils	**Surfactants/ stabilizers**	Caprylocaproyl polyoxyl-8-glycerides [Labrasol1], Polyoxyethylene sorbitan fatty acid esters [Tween1], Polyoxyethylene castor oil derivatives [Cremophor1, Lipocol1], Polyvinyl alcohol, Sorbitan esters [Span1], Tocopherol polyethylene glycol, succinate (TPGS)Macrogol fatty acid glycerides [Gelucire1 44/ 14, Gelucire1 50/13],
	Co-surfactants	Hydroxyl propyl methyl cellulose, Poloxamer, Phospholipids and PEGylated phospholipids,
	co-solubilizers	Polyvinyl pyrrolidone, Bile acids (sodium deoxycholate), Cellulose derivatives, Polyglyceryl-3 dioleate [Plurol1, Oleique1 CC497]
	co-stabilizers	Propylene glycol, Glycofurol, Phospholipids, Oleoyl/ linoleoyl polyoxyl-6-glycerides [Labrafil1], Polyethylene glycol, Triacetin, Ethanol, Diethylene glycol monoethyl ether [Transcutol1 HP]

Telmisartan

Telmisartan is Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension.Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability.One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration.The solubility of Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water. Absolute bioavailability of the Telmisartan was 42-58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration.

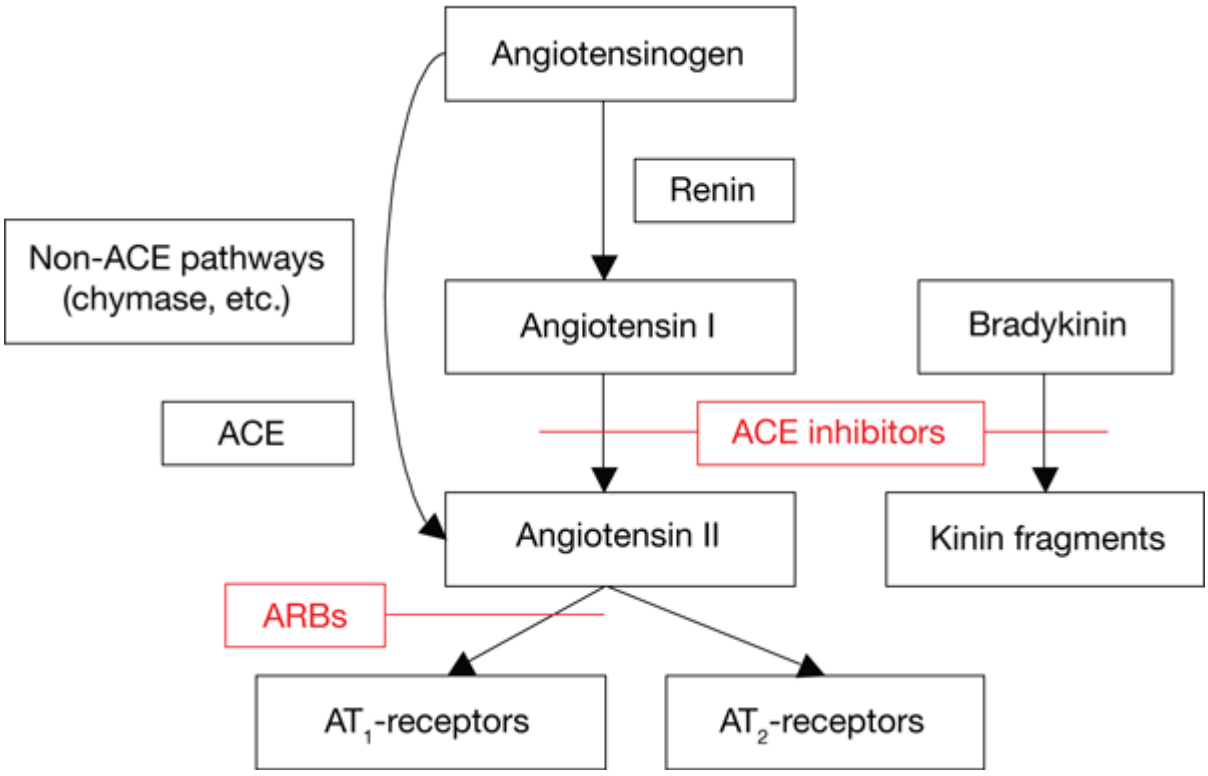


Figure 7: Mechanism of action of Telmisartan

Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance. A many number of approaches have been developed to improve the drug solubility and dissolution of drugs. The solid dispersion is a technique to achieve this goal particularly the poor aqueous soluble drugs in which the drug is incorporated in to water soluble polymeric matrix . In this research the solubility and bioavailability of telmisartan in conjugation with various carriers by using various methods were studied.besides this solubility and dissolution

study, the various evaluation methods were carried out to determine the physico chemical properties of physical mixture and solid dispersions in comparison to pure drug.

Previous researchers have made attempts to improve the aqueous solubility of telmisartan by preparing solid dispersion and solid lipid nanoparticles. The preparation of solid dispersion is easy, but its limitations include stability of the drug and the difficulty of incorporating into solid dispersion in suitable dosage forms. For solid dispersion, the amount of carriers used is often large, and thus if the dose of the active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow.

Moreover, the carriers used are usually expensive and the freeze-drying or spray-drying method requires particular facilities and processes, leading to a high production cost. Though a traditional solvent method can be adopted instead, it is difficult to deal with co-precipitates with a high viscosity. One potential problem with solid lipid nanoparticles formulation is that the drug may favor a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix.

There is a necessity to develop a formulation that would offer rapid dissolution of temisartan and improve its bioavailability and finally therapeutic efficacy. Lipid-based formulation approaches, predominantly the self-emulsifying drug delivery system (SEDDS), illustrate their potential as alternative approaches for the delivery of hydrophobic drugs. Dosing of drug substances that exhibit poor water solubility, but sufficient lipophilic properties in a predissolved state are advantageous in view of the fact that the energy input allied with a solid-liquid phase transition is circumvented, thus overcoming the slow dissolution process after oral intake.

LITERATURE REVIEW

- **Hyma .P1, Anusha Chandra, Abbulu K et al., (2014)** Telmisartan SMEDDS were prepared as a novel technique to improve the solubility of poorly soluble drug. The preformulation studies done clearly indicate good compatibility of the drug with the various excipients used. The reduction of particle size was clearly depicted in the droplet size measurements where the size is reduced to nanometer range, which has led to increase in dissolution rates as shown in the dissolution studies and graph.. Thus it can be concluded that micro emulsion formulation can be used as a successful tool to enhance the bioavailability of the drug, and there formulations can be further tested in vivo by using animal models.

- **Mr. Girish C. Soni, S.K. Prajapati, Nirvesh Chaudhri et al.,(2014)** Ease of manufacture and scale-up is one of the most important advantages that make SNEDDS unique when compared with other novel drug delivery systems, such as solid dispersions, liposomes and nanoparticles. SNEDDS require very simple and economical manufacturing facilities, such as simple mixer with an agitator and volumetric liquid filling equipment for large-scale manufacturing. These SNEDDS are better formulation for drugs with poor solubility. This gives good absorption profiles thus offering high bioavailability for such drugs when administered orally. However the role of nanoscale in improving the transport of drug across biological membranes and therapeutic efficacy is debatable in the case of nanoemulsions. The amenability of converting SNEDDS into solid self-nanoemulsifying systems enables development into solid dosage form. Thus, the solid self-nanoemulsifying system can serve as platform technology for delivering poorly soluble drugs. Although a lot of research is being carried out in this area, other aspects, such as in vito /in vivo correlation, need to be established

- **Parul Jaiswal, Geeta Aggarwal, Sasidharan Leelakumari Harikumar, and Kashmir Singh et al., (2014)** Self-microemulsifying drug delivery system is a vital tool in overcoming the formulation difficulties and improving the oral bioavailability of hydrophobic/lipophilic drugs. In this study, SMEDDS and solid-SMEDDS formulations of poorly water-soluble drug, telmisartan were successfully prepared by the ultrasonication method and adsorbent technique respectively for oral administration. Further, they were assessed for in vitro performances. Among various formulations, F3 in SMEDDS and SF3 in solid-SMEDDS showed promising results in the terms of globule size analysis, self-emulsification time, zeta potential, drug loading efficiency and in vitro drug release. It could be summarized that SMEDDS formed from castor oil, tween 20 and propylene glycol as oil, surfactant and co-surfactant is a promising approach to improve the solubility, dissolution rate and hence bioavailability of telmisartan. The optimized formulations showed significantly improved drug release as compared to pure drug. Solid-SMEDDS were preferred over SMEDDS in terms of stable dosage form. It can be concluded that telmisartan solid-SMEDDS offer more predictable and more extensive drug release/absorption than the corresponding conventional formulations. The results from the study showed the utility of solid-SMEDDS to enhance solubility and bioavailability of sparingly soluble compounds like telmisartan, which can be helpful to reduce dose and related side effects of the drug. The present exploratory work successfully illustrates the potential utility of solid-SMEDDS for the delivery of poor water-soluble compounds.

- **Sindhu Raavi*, Subramanian S, Surya Kiran Vuddisa et al., (2014**) It can be concluded from the experimental study carried out that the formulation of a poorly water soluble drug, Atorvastatin calcium , into a Supersaturated Self Nanoemulsifying Drug Delivery System yields a formulation with the droplets in the nano size range with good zeta potential. The in vitro study of the best formulation AS- 3s SNE tablet with 2% starch as binder showed a 2.5 fold increase in the bioavailability when compared to the marketed formulation.

- **Ali M. Nasr *, Ahmed R. Gardouh , Hassan M. Ghonaim and Mamdouh M. Ghorab et al., (2016)** In this study, a novel liquid SNEDDS consisting of Capryol 90, Cremophor RH40 and Transcutol HP as an oil phase, surfactant and co-surfactant, respectively, was formulated and further developed into a solid SNEDDS by a spray-drying technique using Aerosil 200 as the solid carrier. From this study it was concluded that the prepared liquid SNEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. Study also concluded that S-SNEDDS of IRB prepared by a spray-drying technique using Aerosil 200 as the solid carrier have good flow properties and drug content. This solid SNEDDS preserved the self-emulsification performance of the liquid SNEDDS and gave a faster in-vitro dissolution rate than the crude powder and marketed product. Results of SEM demonstrate that spherical particles of S-SNEDDS can be obtained without agglomeration. Considering the limitations associated with liquid SNEDDS, a solid powder formulation should be a more acceptable form. Furthermore, our results suggest that the S-SNEDDS could be considered and further evaluated for the oral delivery of lipophilic poorly soluble drugs for which an oral route of administration is desirable. In conclusion, Self emulsifying drug delivery systems were a promising approach for the formulation of IRB. S-SNEDDS appeared to be an interesting approach to improve problems associated with oral delivery of IRB. Thus S-SNEDDS can be considered as novel and commercially feasible alternative to current marketed IRB. Finally, the oral delivery of hydrophobic drugs can be made possible by SSNEDDS, which have been shown to substantially improve the oral bioavailability

- **NiraliPadia, Arunkumar Shukla, PragnaShelat et al .,(2015)** In this study, SMEDDS of Telmisartan were prepared and evaluated for their in vitro and in vivo behavior. Prepared liquid SMEDDS was thermodynamically stable with good self emulsification efficiency and having globule size in nanometric range which may be physiologically stable. The optimized formulation consisting of Telmisartan (20mg), Capmul MCM (14.40%w/w), Tween 80 (27.20% w/w) and Propylene glycol (54.40% w/w) exhibited faster release profiles with a rapid rate of emulsification. The optimized SMEDDS formulation of Telmisartan showed a significant increase in oral absorption compared to the marketed product. The exposure (Cmax and AUClast) of developed

SMEDDS was found to be comparatively higher (1.54 fold) than reference marketed product indicating better rate and extent of absorption than reference formulation. Thus, SMEDDS can be regarded as a novel and commercially feasible alternative to current Telmisartan formulations. However, further studies in the higher animals and human beings need to be performed before this formulation can be commercially exploited.

- **Rahul S. Narkhede, Kishor N. Gujar, Vaishali M. Gambhire* et al ., (2013)** The present study has clearly showed the potential utilization of S-SNEDDS for formulating NEB with improved aqueous solubility, stability and in-vitro drug release. The S-SNEDDS with relatively high cryoprotectant effect was prepared which self-emulsified easily with mean emulsion droplet size of 156.34 nm. Stability study and cloud point study confirmed that the S-SNEDDS had no dilution effect and was stable at 0.1 N HCl and phosphate buffer 6.8 without any change in emulsion droplet size.

- **Ali Nasr*, Ahmed Gardouh , and Mamdouh Ghorab , et al ., (2016)** In this study, liquid SNEDDS was formulated and further developed into solid SNEDDS by a spray-drying technique using Aerosil 200 as the solid carrier. From this study, it was concluded that the prepared liquid SNEDDS was thermodynamically stable with good self-emulsification efficiency and having globule size in the nanometric range which may be physiologically stable. It was also concluded that S-SNEDDS preserved the self-emulsification performance of the liquid SNEDDS and gave a faster in vitro dissolution rate than the crude powder and marketed product. Furthermore, our results suggest that S-SNEDDS could be considered and further evaluated for the oral delivery of lipophilic poor soluble drugs for which an oral route of administration is desirable. In conclusion, self-emulsifying drug delivery systems represented a promising approach for the formulation of OLM. S-SNEDDS appeared to be an interesting approach to improving problems associated with oral delivery of OLM. Thus, S-SNEDDS can be considered as a new and commercially feasible alternative to current marketed OLM. Finally, the oral delivery of hydrophobic drugs can be made possible by S-SNEDDS, which have been shown to substantially improve the oral bioavailability.

- **Payal Gupta, Pramod Kumar Sharma, Nitin Kumar, Yogesh Pawar, Jitendra Gupta et al., (2014)** SNEDDS is a promising approach for BCS class II or IV and drug compounds with poor aqueous solubility. The method used for lipophilic drugs where resulting emulsification gives faster dissolution rates. The oral delivery of hydrophobic drugs can be made possible by SNEDDS which have been shown to substantially improve oral bioavailability with future development of this technology. SNEDDS will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

OBJECTIVE

- To prepare SNEDDS of Telmisartan
- To convert Liquid SNEDDS to Solid – SNEDDS form
- To characterize the prepared SNEDDS for the size, self emulsification time, drug content
- To improve the *in vitro* dissolution rate of the solid SNEDDS

PLAN OF WORK

PHASE – I

- Drug profile
- Polymer and excipient profile

PHASE- II

- Preformulation studies
    a. Identification of drug
        1. Melting point determination
        2. Infrared studies
    b. Solubility studies
    c. Calibration curve

PHASE - III

- Preparation of liquid SNEDDS
- Conversion of liquid SNEDDS to solid SNEDDS

PHASE- IV

Characterization of nano particle formulation

- Particle size determination
- Zeta potential
- SEM analysis
- Self-emulsification time

PHASE- V

- *In vitro* release study

DRUG PROFILE OF TELMISARTAN

Telmisartan is in the drug class of angiotensin receptor blockers (ARBs) and is prescribed for the treatment of high blood pressure, reducing the risk of heart attack, stroke, or death from cardiovascular causes,

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects

Structure

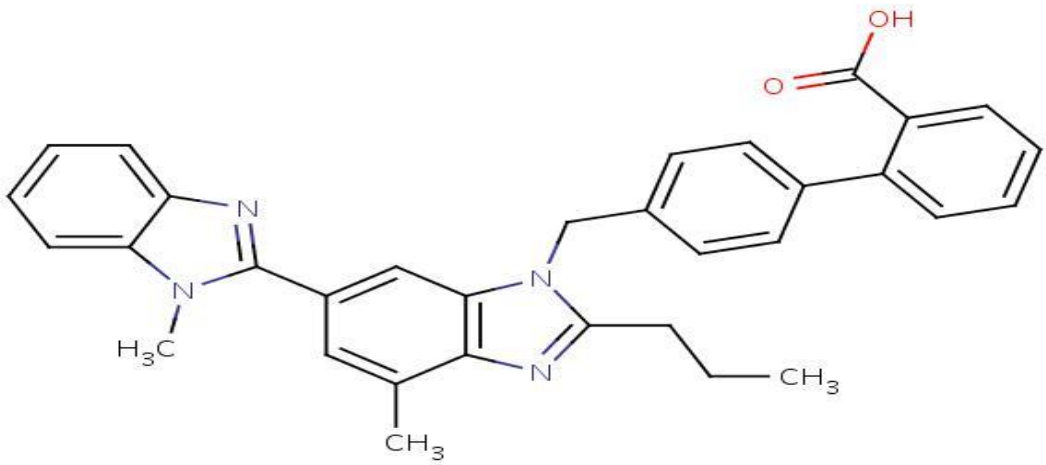


Figure 8: Structure of Telmisartan.

Chemical Name:-

[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl] 1,1 ‘ biphenyl] – 2 carboxylic acid.

Molecular Formula:- $C_{33}H_{30}N_4O_2$

Molecular Weight:- 514.61

Description:- White to off-white crystalline powder.

Melting range:- Between 265.0ºC and 272.0ºC

Solubility:- Practically insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride, it dissolves in 1M sodium hydroxide.

Partial coefficient:- The Octanol/buffer partial coefficient (log P) for Telmisartan is approximately 3.20

Storage & Stability:- Stored in well-closed, light-resistant containers at 5-30°C. When stored under these conditions, Telmisartan generally is stable for 24 months after the date of manufacture.

Indication:- For the treatment of hypertension

Clinical Pharmacology:-

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT_1 receptor subtype. New studies suggest that telmisartan may also have PPARã agonistic properties that could potentially confer beneficial metabolic effects. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

Mechanism of Action:-

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels.

Pharmacokinetic properties;
Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal eliminate ion half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

EXCIPIENTS PROFILE

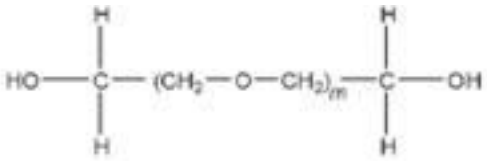
POLYETHYLENE GLYCOL

Synonyms : Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG;Pluriol E; polyoxyethylene glycol.

Chemical Name : a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula : $HOCH_2$ (CH_2OCH_2) mCH_2OH where m represents the Average number of oxyethylene groups.

Structural Formula:



Molecular Weight : 3000 to 4800 g/mol

Functional Category : Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant

Description : The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycolgrades 200–600 are liquids; grades 1000 And above are solids atambient temperatures. Liquid grades (PEG 200–600) occur as clear, colourless or slightlyyellow-colored, viscous liquids. They have a slight but characteristic odour and a bitter, slightly burning taste

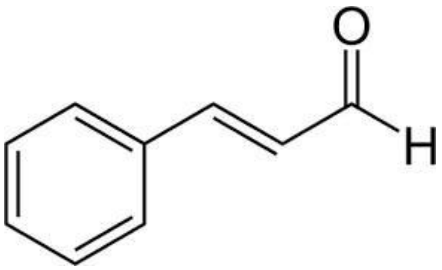
CINNAMON OIL

Synonyms : Cassia oil,cinnamon bark oil,cinnamomum zeylanicum,bloom bark oil

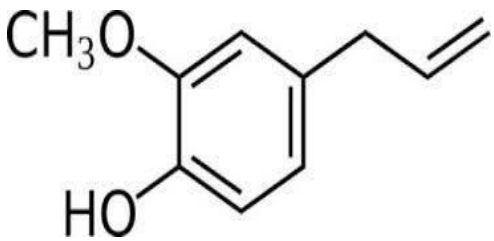
Description : Cinnamon bark oil posses the delicate aroma of the spice and a sweet pungent taste. Its major constituent is cinnamaldehyde but other minor components impart the characteristic odour and flavour. It is employed mainly in the flavouring industry where it is used in meat and fast food seasoning ,sauces,pickles,baked goods,cola type drinks,confectionary and in dental and pharmaceutical preparations. Perfumery applications are far fewer than in flavours because the oil has some skin sensitising properties ,but is can be used limitedly in a few perfumes.

Composistion : The primary constituents of the essential oil are 65% to 80% of cinnamaldehyde and lesser percentages of the other phenols and terpenes including eugenol , trans cinnamic acid ,hydroxy cinnamaldehyde , cinnamyl alcohol and its acetate ,limolene, alpha terpinol ,tannins ,mucilage ,oligomeric procyanidins and trace amounts of coumarin

Structure :



Cinnamaldehyde



Eugenol

Apperence	**:**	Liquid
Colour	**:**	Yellow
Density	**:**	1.03 g/ml at 25^{o} C
Solubility	**:**	Soluble in alcohol , insoluble in water
Uses	**:**	Flavouring agent , germicide , fungicide , local stimulant , aromatic,Astringent carminative

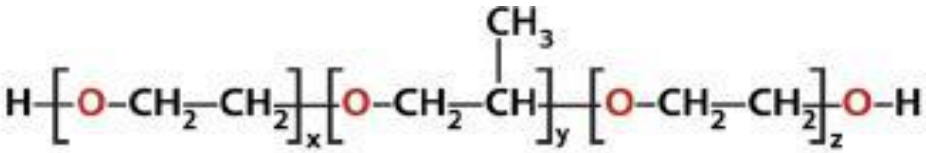
PLURONIC F 127

Synonyms : Polyethylene-propylene glycol copolymer

Chemical name : α-hydro-o-hydroxypoly(oxyethylene)poly (oxypropylene) poly-(oxyethylene) block copolymer

Empirical formula : The poloxamer polyols are a series of closely related block copolymers of ethylene oxide conforming to the general formula

Structural formula :



Pluronic F127

Molecular weight : 12500 daltons

Functional category : Non ionic surfactant ; emulsifying agent ;solubilising agent tablet lubricant ; anti foaming agent

Description : Pluronic F 127 generally occur as white ,waxy ,free flowing prilled granules or as cast solids .they are practically odourless and tasteless.

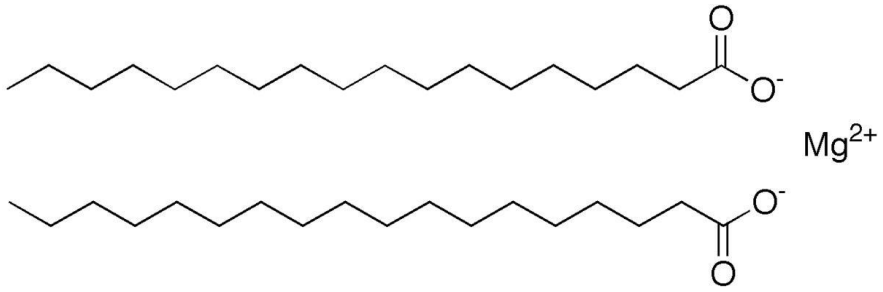
MAGNESIUM STEARATE

Description : Light white,very fine, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste

Synonyms : Magnesium distearate, magnesium octadecanoate, acid, magnesium salt, stearic acid, dibasic magnesium stearate

Chemical Name : Octadecanoic acid magnesium salt

Structural formula



Molecular Weight : 591.24 g/mol

Molecular Formula : $[CH_2(CH_2)_{16}COO_2]Mg$

Melting Point : 117-150° C

Solubility : Slightly soluble in benzene and warm ethanol and practically not soluble in ethanol

Stability and Storage : Stable material and should be stored in a well closed dry container in a cool, dry place

Safety : Non toxic for oral administration and consuming higher quantity will lead to produce laxative effect

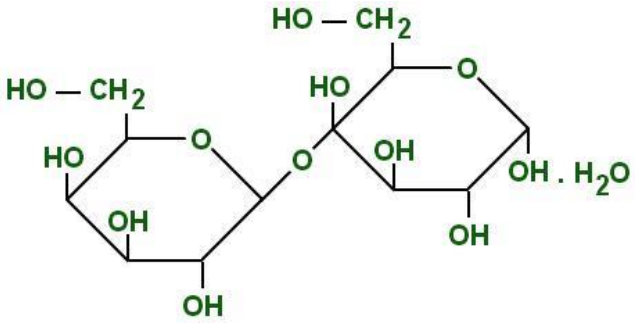
Related Substances : Calcium stearate, stearic acid, zinc stearate

LACTOSE

Synonyms : Arose 25, milk sugar, lactosum mono hydricum monohydrate lactose.

Chemical name : D-(+)-lactose 1-hydrate , D- lactose mono hydrate

Structural formula :



Molecular formula : $C_{12}H_{24}O_{12}$

Molecular weight : 360.31g/mol

Melting point : 215° C

Solubility : freely soluble in water, slightly soluble in alcohols and insoluble chloroform.

Stability : keep container tightly closed in a cool well ventilated area.

Storage : Do not store above 23° C

Safety : kept away from heat, sources of ignition and oxidizing agents . Do not ingest or breathe dust.

Related substances : lactulose , alpha lactulose , alpha D- lactose monohydrate,spray dried lactose, anhydrous lactose

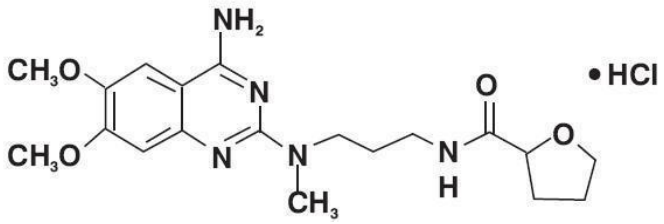
Application : lactose is widely used as a filler or filler-binder in pharmaceutical tablets by the direct compression method.

TALC

Synonyms : Talcum, stealite, shelleck

Chemical name : Hydrous magnesium silicate

Structural formula :



Molecular weight : 379.27 g/mol

Molecular formula : $H_2 Mg_3 O_{12} Si_4$

Melting point : 800°C

Solubility : Insoluble in water and ethanol, very slightly soluble in mineral Acids

Stability and storage : Talc is stable and store in dry place in well closed contained or Bags

Safety : At levels of 1000mg/m^3 ,talc is considered as immediately dangerous to use and hazardous to health.

Related to sustances : Hydrous magnesium silicate .

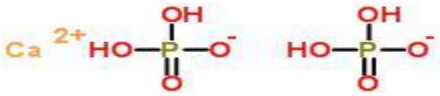
Applications : Anti-caking agents,coating agents,lubricating agents and release agent, filler aid and dusting powder.

DICALCIUM PHOSPHATE

Synonyms : calcium hydrogen phosphate, phosphoric acid ,calcium salt

Appearance : white granular powder

Structural formula :



Molecular formula : $CaHPO_4$

Molecular weight : 172.03 g/mol

Density : 2.31 g/cm^3

Solubility : Soluble in ammonium citrate, citric acid, insoluble in water

Storage : Store at room temperature.

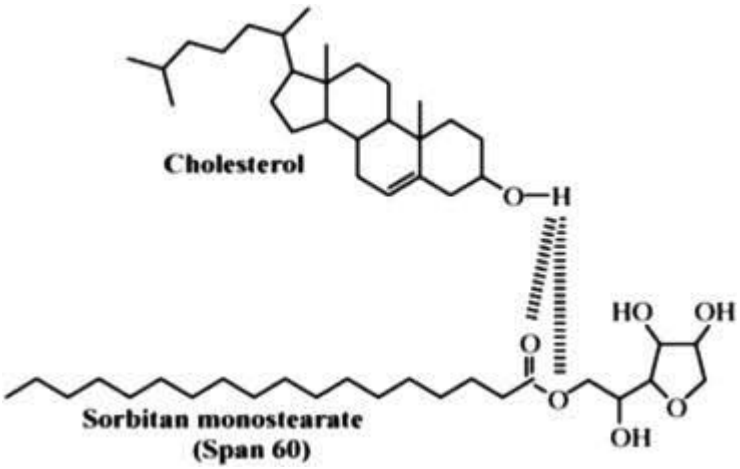
Applications : Flowing agent, tablet filler, food additive, polishing agent, biomaterial

SPAN 60

Molecular formula : $C_{24}H_{46}O_6$

Chemical name : Sorbitian monostearate

Structural formula :



Melting point : 57 ˚C

Flash point : >230 ˚F

Molecular weight : 43.6 g/mol

Solubility : Soluble in ethanol,isopropanol,vegetable oil and mineral oil
Insoluble in water.

Stability : Stable. combustible. incompatible with oxidizing agents

Storage : Store below 30˚C

MATERIALS & INSTRUMENTS

Table 2.1: List of chemicals used

INGREDIENTS	VENDER
Telmisartan	Gifted sample
Cinnamon oil	S.D. Fine chemicals
Polyethylene glycol 400	Sigma Aldrich
Pluronic F 127	Sigma Aldrich
Micro crystalline cellulose	Sigma Aldrich
Lactose.LR	S.D.Finechemicals.ltd
Magnesium stearate. LR	Otto chemical reagents
Talc.LR	Lobachemie Ltd.,Mumbai
Dicalcium Phosphate	Sigma Aldrich

LIST OF EQUIPMENT USED

Table 2.2: List of Equipments used

Equipment	Make and Model
pH meter	LI-120 , ELCO
Compression Machine	Rimek, 10 station, B- Tooling
UV spectrometer	UV 1650 PC SHIMADZU
FT/IR spectrometer	JASCO 4100-FT/IR , FT/IR 8400 Shimadzu
Dissolution apparatus	USP Dissolution apparatus paddle 2 method-240V
Centrifuge (ultra)	EPPENDROF ,5415 R , GERMANY
Magnetic stirrer	2MLH , REMI Insrument
Bath sonicator	Sonics – 230 10v
Sieves	Jayant scientific , Mumbai
Electronic balance	ELB 300 , shimadzu , Philippines
Cyclo mixer	CM 101 REMI
Particle size and zeta potential analyzer	MALVERN zeta sizer ZS90
Phase contrast Microscopy	Leica, S40 , 230 10 V, 5W
Scanning Electron Microscope	JEOL, Japan- JSM 6360

PREFORMULATION STUDIES

MELTING POINT

A capillary tube was sealed with a Bunsen burner and it was filled with the drug telmisartan through the open end. The drug – filled capillary tube was placed in the melting point apparatus and temperature at which the drug started to melt was noted.

SOLUBILITY STUDIES

1g of the drug was dissolved in 1ml, 10ml, 30 ml and 100ml of various solvents depending upon its solubility. The resulting solubility was compared with the solubility limits specified in the Indian pharmacopeia

DETERMINATION OF LAMBDA MAX

10 mg of drug was dissolved in 10 ml of methanol to prepare stock solution – A of concentration 1mg/ml. 1ml of stock-A was further diluted to 100 ml to get stock-B of concentration 20 mcg/ml. This solution was scanned from 200-400 nm in a UV spectrophotometer to determine the lambda max.

STANDARD CURVE

10mg of drug was dissolved in 100ml of methanol to get a stock solution –A of concentration 100mcg/ml. 0.1ml of stock –A was diluted to 10 ml to give a stock – B. A serial dilutions of the stock-B were done to get solutions of concentrations 1, 2, 3, 4, 5, 6, 7,8 mcg/ml. These solutions were analyzed in the UV spectrophotometer at the 296 nm. A calibration curve was plotted with concentration on x-axis and the absorbance on the y-axis, the correlation coefficient was also calculated.

STANDARD GRAPH

The linearity was obtained between 1-10 mcg/ml of telmisartan and the regression value was found to be 0.99113

Table 2: Calibration curve of Telmisartan

Concentration (mcg/ml)	Absorbance at 296 nm
1	0.076
2	0.296
3	0.386
4	0.493
5	0.626
6	0.748
7	0.915
8	1.064

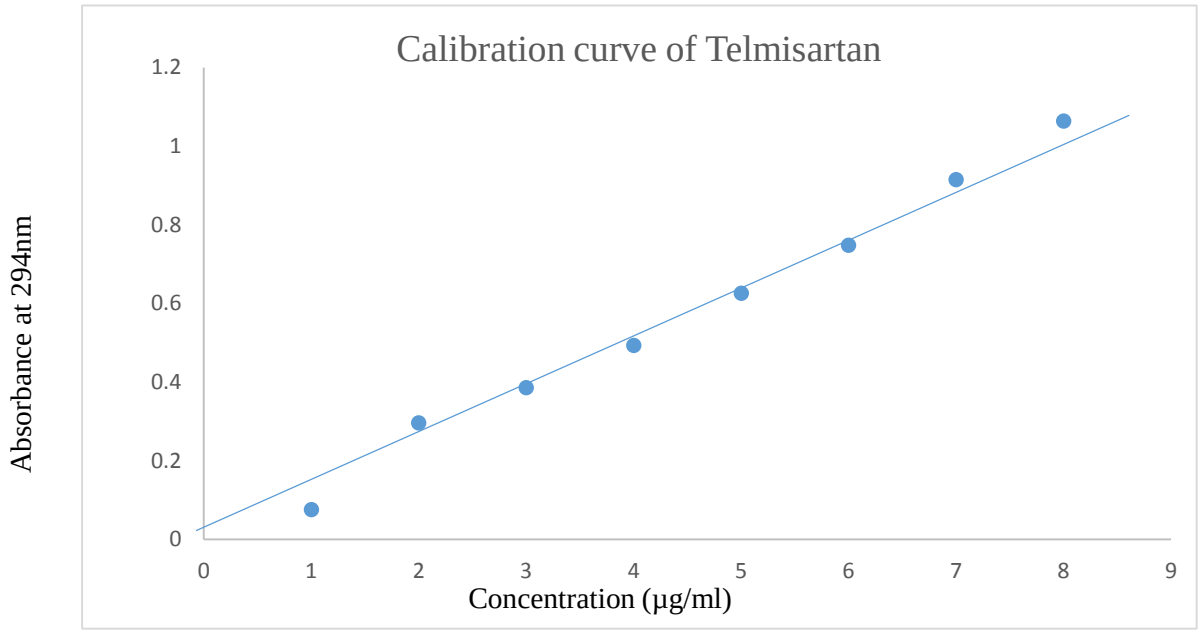


Figure 9: Calibration curve of Telmisartan

METHODOLOGY

Screening of components

Solubility studies

The solubility of Telmisartan in various oils, surfactants and co-surfactants was done by the vial shake method. An excess of drug was added to the vial containing 5ml of the oil/surfactant and was sealed with an aluminum foil. The sealed vial was heated at 40°C and then centrifuged at 15,000 rpm for 10 mins. The insoluble drug was removed by filtering it and the resulting solution was analyzed in the UV spectrophotometer.

Emulsification study

Surfactant

300 mg of the surfactant was mixed with 300 mg of the selected oil, heated to 50°C and diluted to 50 ml with water. The ease of emulsification was observed by the number of flask inversions required for the formation of an emulsion. The prepared emulsions were analyzed in the UV spectrophotometer for their percentage transparence at 650 nm using distilled water as blank. They were also observed visually for any signs of phase separation or turbidity.

Co-surfactant

100 mg of co-surfactant, 200 mg of surfactant and 300 mg of the selected oil were taken and heated to 50°C and 300 mg of this mixture was diluted to 50 ml. This was assessed for the ease of emulsification by the above procedure.

Pseudo ternary phase diagrams

The surfactant and co-surfactant were mixed in different ratios and was added to oil phase in varying proportions. It was then titrated with water until the mixture turned clear. The values were then plotted in Chemix software to identify the nanoemulsification region

Preparation of SNEDDS

The drug was weighed to 80mg and was mixed with the specified amount of oil. To this the specified amount of the surfactant and co surfactant were added. It was heated to 40°C and sonicated for 15 mins, after which it was stored at room temperature.

Table 3: Composition of Telmisartan SNEDDS formulation

Formulation code	Drug (mg)	Oil (cinnamon oil) (ml)	Surfactant (PEG-400) (ml)	Cosurfactant (propylene glycol) (ml)
FT 1	1	0.3	0.5	0.2
FT 2	1	0.2	0.3	0.5
FT 3	1	0.5	0.3	0.2
FT 4	1	0.2	0.4	0.4
FT 5	1	0.4	0.2	0.4
FT 6	1	0.3	0.5	0.2
FT 7	1	0.3	0.3	0.4
FT 8	1	0.5	0.2	0.3
FT 9	1	0.4	0.4	0.2
FT 10	1	0.2	0.5	0.3

Formulation code	Drug (mg)	Oil (cinnamon oil)(ml)	Span 60 (mg)	Pluronic F 127 (mg)
FT 11	80	3	400	300
FT 12	80	2	400	400
FT 13	80	2	350	350

Brij – 72 was not used as surfactant because brij – 72 forms insoluble aggregates when preparing formulations

T2, T4&T9 are selected based on formation of emulsion. After few days emulsion goes to instability due to improper selection of surfactants. Due to instability of emulsion cosurfactant was changed and replaced with pluronic F 127 because it has higher percentage of transmittance after propylene glycol.

Conversion of liquid SNEDDS to solid SNEDDS:

Liquid SNEDDS was taken and mixed with adsorbents avicel pH 101 until free flowing powder was obtained .The powder was then mixed with additives , dicalcium phosphate as binding agents in suitable proportions. 13 mm punch and die cavity were used for punching to yield self nanoemulsifying tablets of telmisartan.

Evaluation parameters of liquid SNEDDS:

Visual observation:

The formulation were diluted and made to stand for 24 hours at 37° C. They were observed for phase separation and turbidity.

Self-emulsification time:

1ml of formulations was added to 100 ml of distilled water at 37° C being agitated at 100 rpm. The time required for the formation of a milky emulsion was noted**.**

Table 4: Grades for the visual assessment of self nano emulsifying formulation

Grade	Visibility
I	Clear or slightly bluish white in appearance within I Minute
II	Slightly less clear ; bluish white in appearance < 2 minutes
III	Milky in appearance within 3 minutes
IV	Dull white which is slightly in appearance , slow to emulsify > 3 minutes
V	Turbid in appearance > 3 minutes

Droplet size and zeta potential :

1ml of formulation was diluted to 100 ml with distilled water and sonicated for 15 minutes .the resulting nano-emulsion was checked for droplet size and zeta potential in a particle size analyzer (Malvern zetasizer). The average droplet size and zeta potential was determined.

Drug content:

1ml of formulations were taken and diluted sufficiently .these solutions were then analyzed in the UV spectrophotometer. The drug concentration present was extrapolated from the standard graph. The drug content was calculated using the below formula.

Drug content = concentration X dilution factor X correction factor X volume of formulation.

Robustness to dilution:

The formulations were diluted to 10 ml, 50 ml, and 100 ml and were observed over a period of 24 hours for phase separation or signs of precipitation.

Morphological studies:

Scanning electron microscopy : The morphology and size of the prepared SNEDDS was observed by SEM .samples were fixed on a brass stub using double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold and SEM images were recorded at 15 KeV accelerating voltage.

EVALUATION OF SOLID – SNEDDS

Micrometrics properties of s-SNEDDS of telmisartan

Characterization of telmisartan loaded S-SNEDDS

Angle of repose (θ)

The angle of repose of S-SNEDDS was determined by funnel method. Accurately weighed sample were taken in afunnel. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of S-SNEDDS powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of thepowder cone was measured and angle of repose calculated using the following equation

$$\tan \theta = h/r$$

Where; h = height of the heap, r = radius of the heap

Bulk and tapped density

Both bulk density (BD) and tapped density (TD) were determined. A quantity of 2 g of S-SNEDDS was introducedinto a 10 mL measuring cylinder. Initial volume was observed, and then the cylinder was allowed to fall under itsown weight onto a hard surface from a height of 2.5 cm at 2 second intervals. The tapping was continued until nofurther change in volume was noted. Bulk density and tapped density were calculated using the following equations

BD = Weight of powder / Bulk Volume

TD = Weight of powder / Tapped Volume

Compressibility Index

The compressibility of the S-SNEDDS granules was determined by Carr's Compressibility Index as follow

Carr's Compressibility Index (%) = [(TD-BD) / TD] X 100

Hausner ratio

It is the ratio of tapped density to bulk density. It gives an idea about the flow characters of powder particles and can be calculated as follow

Hausner ratio = TD / BD

Evaluation of telmisartan SNE tablet:

Weight variation

10 tablets were selected randomly and weighed.The average weight was also seen. The weight variation between the individual weight and average weight was calculated. The weight variation should conform to the limits.

Table 5: IP limits for weight variation

Average weight of the tablet (mg)	Maximum percentage deviation allowed (%)
<130 mg	10
130-324	7.5
>324	5

Hardness

Tablet hardness is the force required foe breaking the tablet in a diametric compression test. A tablet was placed between the anvils of the tester and the crushing strength is noted . normal hardness ranges from 4-6 kg/cm^2

Friability

10 tablets were weighed and placed in a friabilator. It was operated at 25rpm for 4 mins or 100 revolutions dropping the tablet from a 6 inch height during revolutions. The percentage friability was calculated by

Percentage friability = (initial weight – final weight) / initial weight X 100

Disintegration

It is the time in which tablets will disintegrate into particles which will pass through a mesh screen size 10. The disintegration tester contains a basket a basket rack with 6 tube with 10 mesh screen at the bottom. The basket is immersed in a medium at 37° C usually.

IN-VITRO DISSOLUTION STUDIES

Instrument	:	USP XXIV dissolution rate test apparatus
Type	:	paddle type
Medium	:	0.1N HCL buffer pH 1.2 – 900 ml
Temperature	:	37 ± 0.5°C
Testing time	:	60 mins
Sample withdrawal volume	:	5 ml at specified intervals
Sample	:	telmisartan S-SNE tablet

USP 24 paddle instrument (ELECTRO LAB TDT – 06 P)

The dissolution of the tablets was performed in 0.1N HCL buffer pH 1.2 at 37° C at 75 rpm and a stirrer depth of 25mm. the sampling intervals were 5,10,15,30,45,60,75 and 90 minutes. 5 ml of fresh buffer solution was replaced after each withdrawal. The sample was then filtered and analyzed spectrophotometrically. The experiments were performed in triplicate and the mean values are reported.

RESULTS AND DISCUSSIONS

PREFORMULATION

Melting point

The melting point was found to be 272˚C which confirms the identification of the drug

Solubility studies

Solubility of Telmisartan in different solvents are

Water – insoluble

Ethanol – slightly soluble

Methanol – soluble

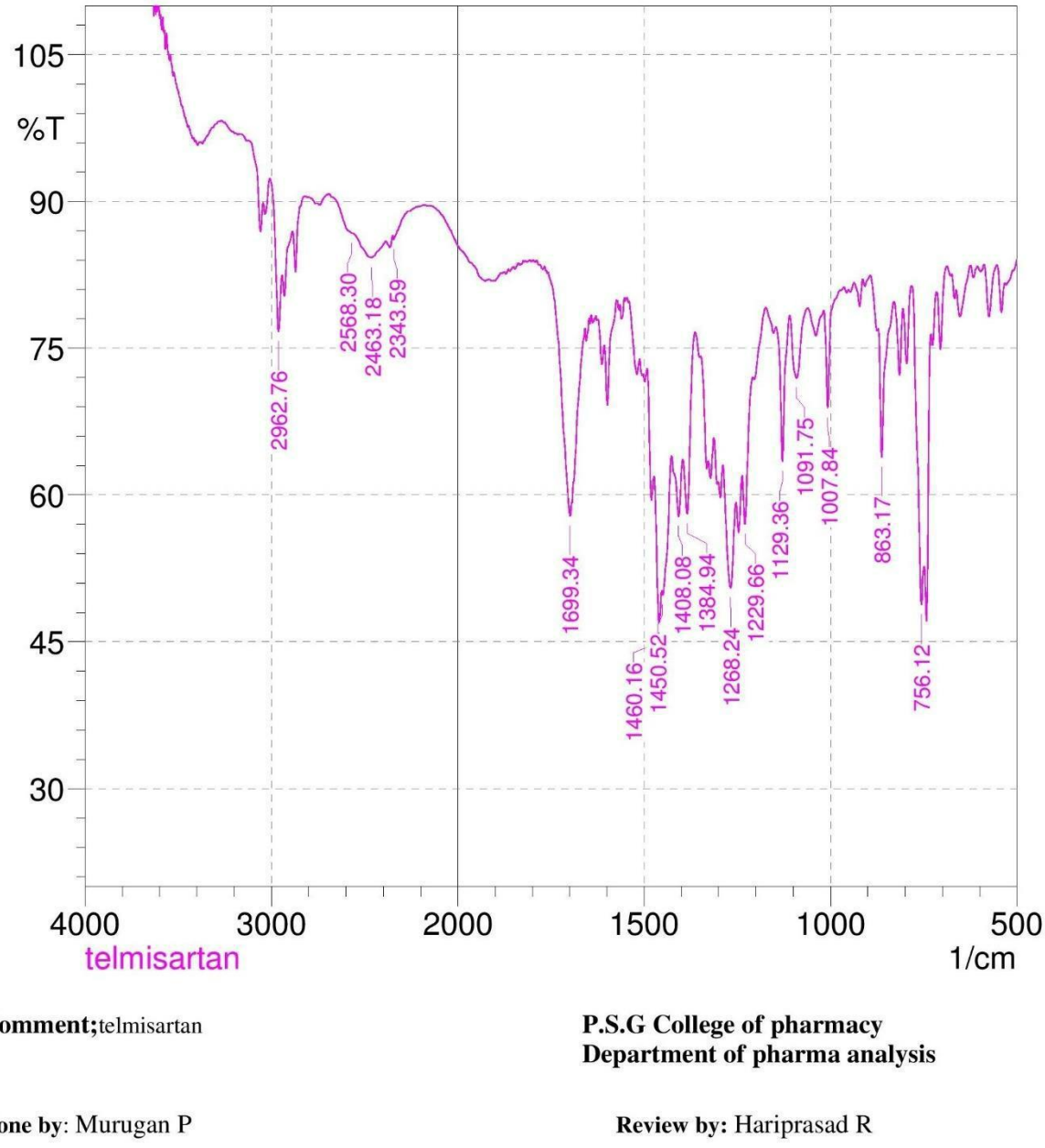
Dissolves in 1M sodium hydroxide

LAMBDA MAX

The diluted stock which was scanned for maximum wavelength the peak at 296 nm .this was selected and was used for further studies

FT/IR data of Telmisartan

Figure 10: FT-IR data of Telmisartan



Comment;telmisartan

P.S.G College of pharmacy
Department of pharma analysis

Done by: Murugan P

Review by: Hariprasad R

Table 6: FT- IR data of Telmisartan

S.no	Wave number cm^{-1}	Assignment of group
1	1460	Methyl C-H asymmetric bond
2	1408	Carboxylic acid
3	1384	Aliphatic nitro compounds

FT/IR data of Pluronic F 127

Figure 11: FT-IR data of Pluronic F 127

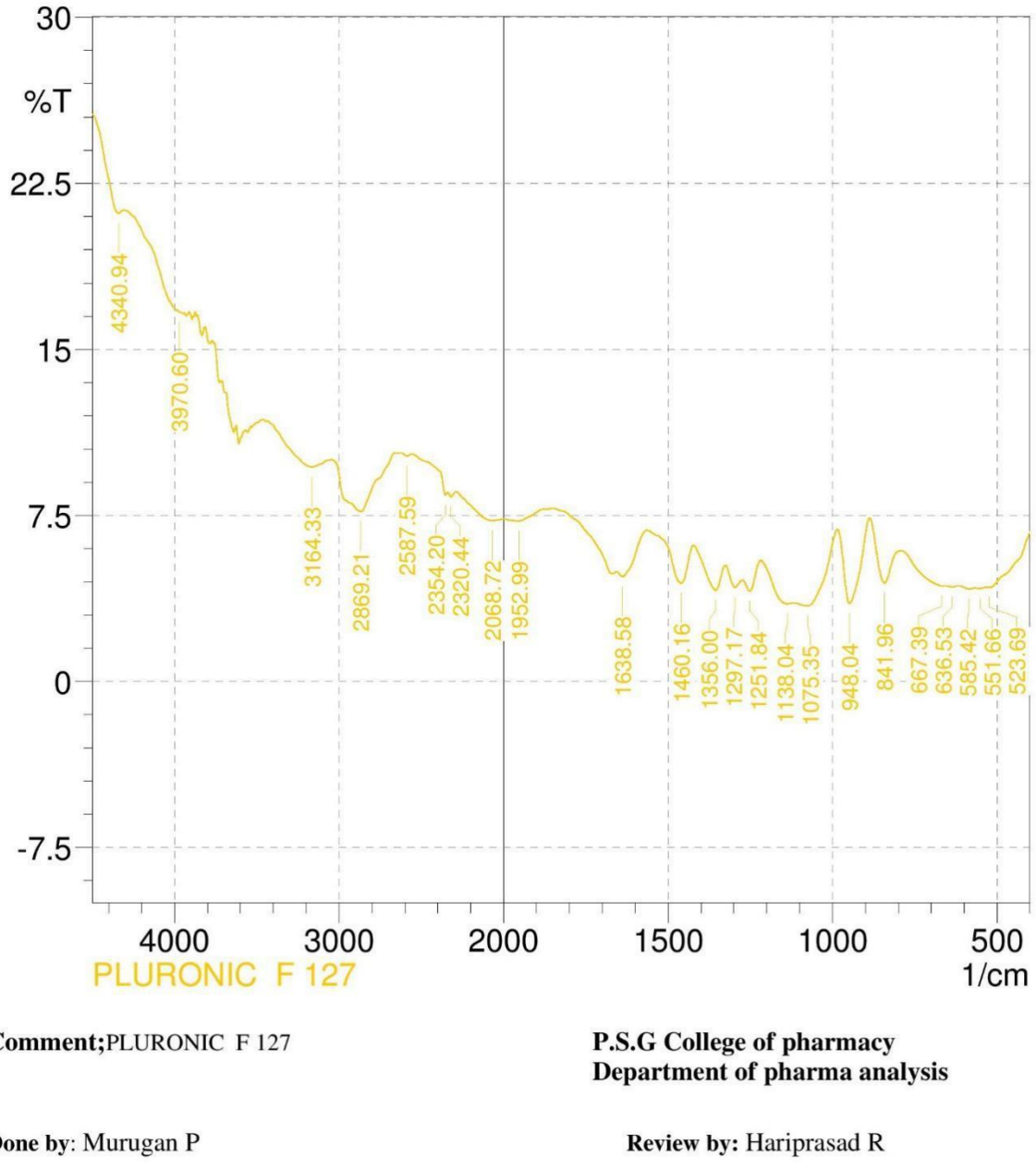
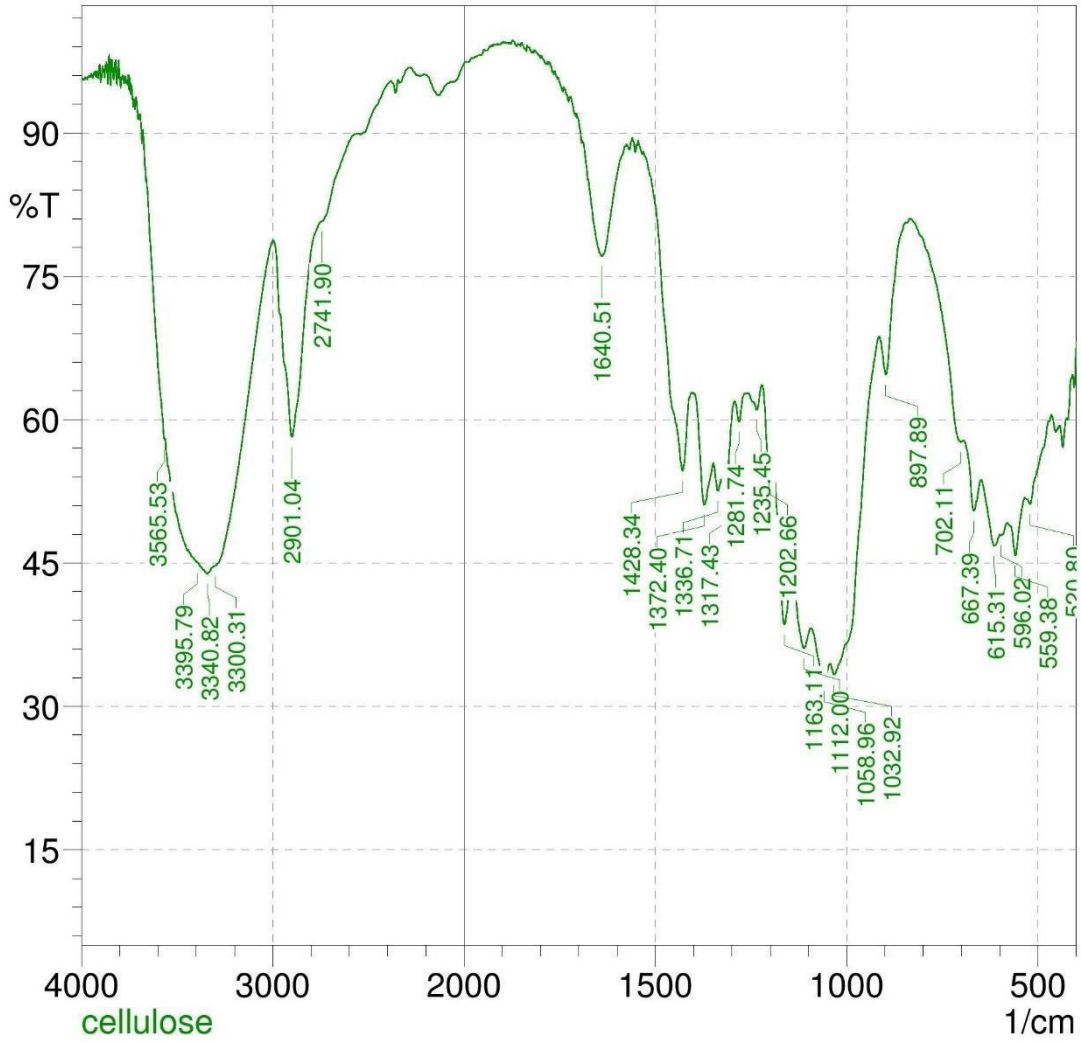


Table 7: FT- IR data of Pluronic F 127

S.No	Wave Number cm^{-1}	Assignment of group
1	3362	O-H stretching
2	2927	C-H stretch
3	1455	C-H bend
4	1299	C-O stretch

FT/IR Data of Microcrystalline cellulose

Figure 12: FT-IR data of Microcrystalline cellulose



Comment;cellulose

P.S.G College of pharmacy
Department of pharma analysis

Done by: Murugan P

Review by: Hariprasad R

Table 8: FT- IR data of Microcrystalline cellulose

S.no	Wave number cm^{-1}	Assignment of group
1	668	C-H bend
2	1032	0-H stretching
3	3565	Hydroxyl group,H bonded O-H stretch
4	1640	Aromatic combination bands

FT-IR DATA OF SPAN 60

Figure 13: FT-IR data of Span 60

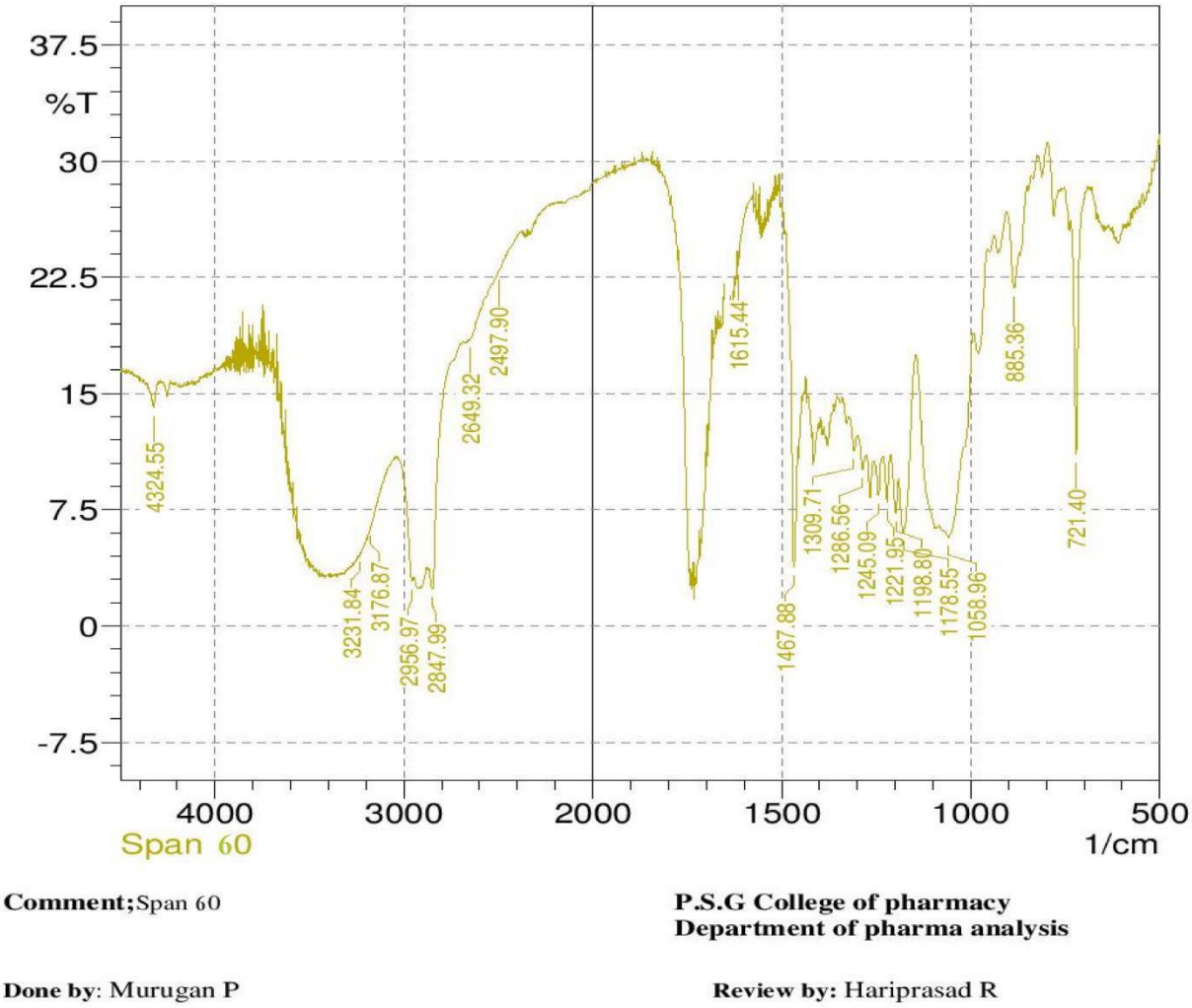


Table 9: FT- IR data of span 60

S.no	Wave number cm^{-1}	Assignment of group
1	721	Aromatic C-H out plane bend
2	1058	Alkyl substituted C-O stretch

FT – IR DATA DRUG + EXCIPIENTS

Figure 14: FT-IR data of Drug&Excipients

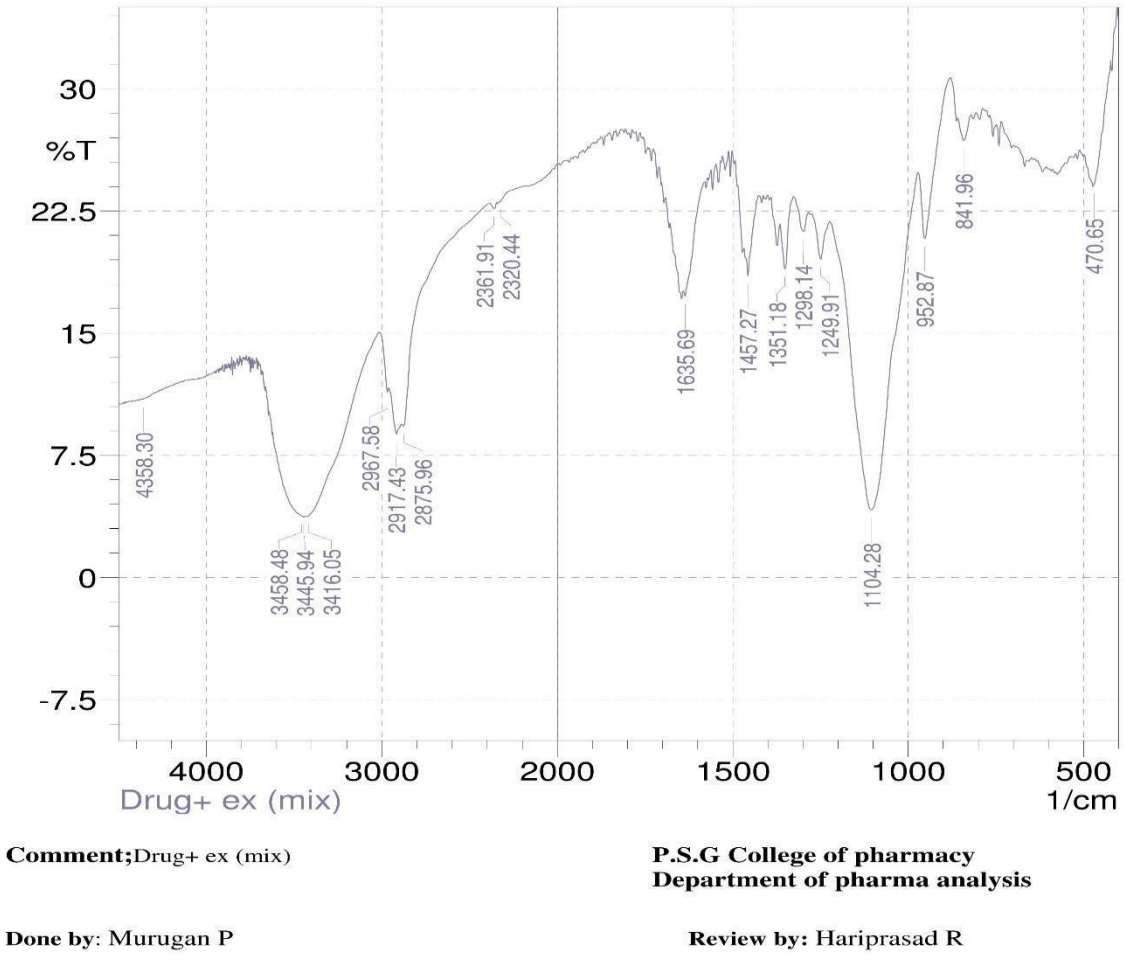


Table 10: FT- IR data of Drug&Excipients

S.no	Wave number cm^{-1}	Assignment of group
1	3164	Normal polymeric OH stretch
2	1460	Methyl C-H asymmetric bond
3	3458	O-H stretch
4	1640	Aromatic combination bands

STANDARD GRAPH

The linearity was obtained between 1-10 mcg/ml of telmisartan and the regreesion value (r^2) was found to be 0.99113

Table 11: Calibration curve of Telmisartan

Concentration (mcg/ml)	Absorbance at 296 nm
1	0.076
2	0.296
3	0.386
4	0.493
5	0.626
6	0.748
7	0.915
8	1.064

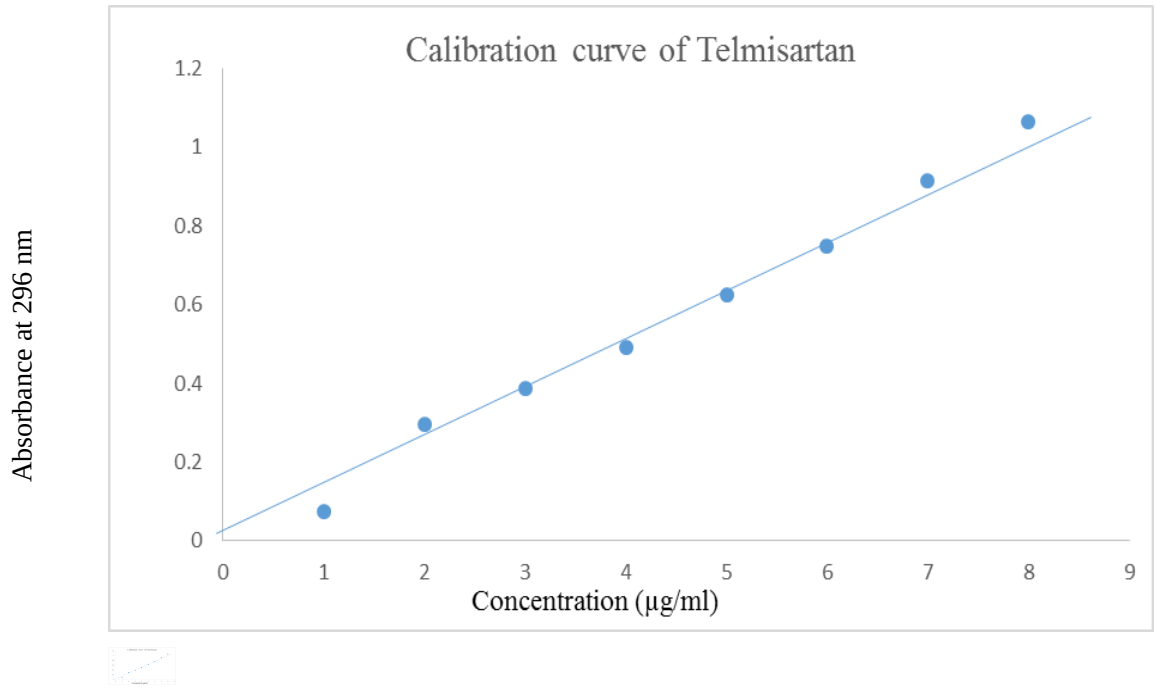


Figure 15 : Calibration curve of Telmisartan

FORMULATION OF S-SNEDDS

The components of the SNEDDS have to be selected with care in order to avoid precipitation of the drug during the shelf life. Therefore the solubility studies of Telmisartan in oils and surfactants were carried out. The results are shown in the figure. Telmisartan was highly soluble in cinnamon oil among the lipids, 25±1.43 mg ml. The various solubilities are depicted in the figure.

Table 12: Solubility studies in oil

S NO	Vehicle	Solubility (mg/ml)
1	Olive oil	7.21
2	Cotton seed oil	8.36
3	Cinnamon oil	25
4	Corn oil	4.89

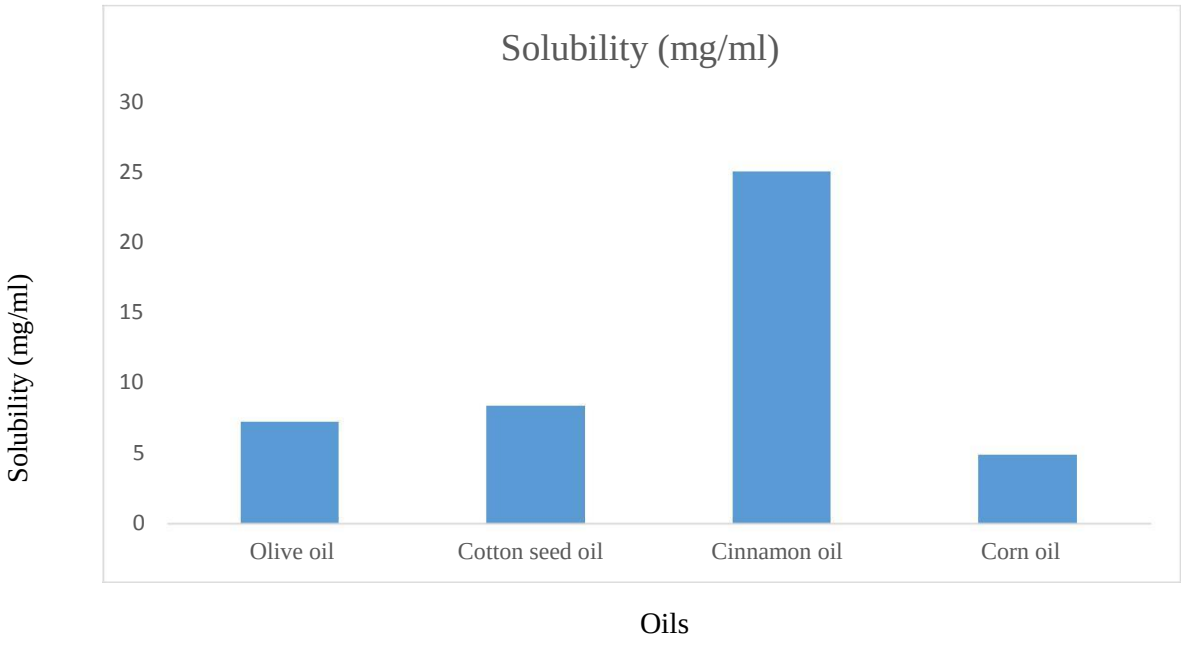


Figure 16: Solubility studies in oil

Screening of Surfactants

300 mg of the surfactant was mixed with 300 mg of the selected oil, heated to 50°C and diluted to 50 ml with water. The ease of emulsification was observed by the number of flask inversions required for the formation of an emulsion. The prepared emulsions were analysed in the UV spectrophotometer for their percentage transparence at 650 nm using distilled water as blank.

They were also observed visually for any signs of phase separation or turbidity. Based on the percentage of transmittance surfactant has selected for formulation. Brij 72 forms insoluble aggregates so we select the propylene glycol, Span 60, PEG 400 and Pluronic f 127

Table 13: Percentage transmittance of surfactants

Surfactant	Percentage of transmittance
Span 40	18.12
Span 60	50.35
Brij 72	63.7
PEG 400	71.72
Propylene glycol	80.61
Pluronic f 127	66.65

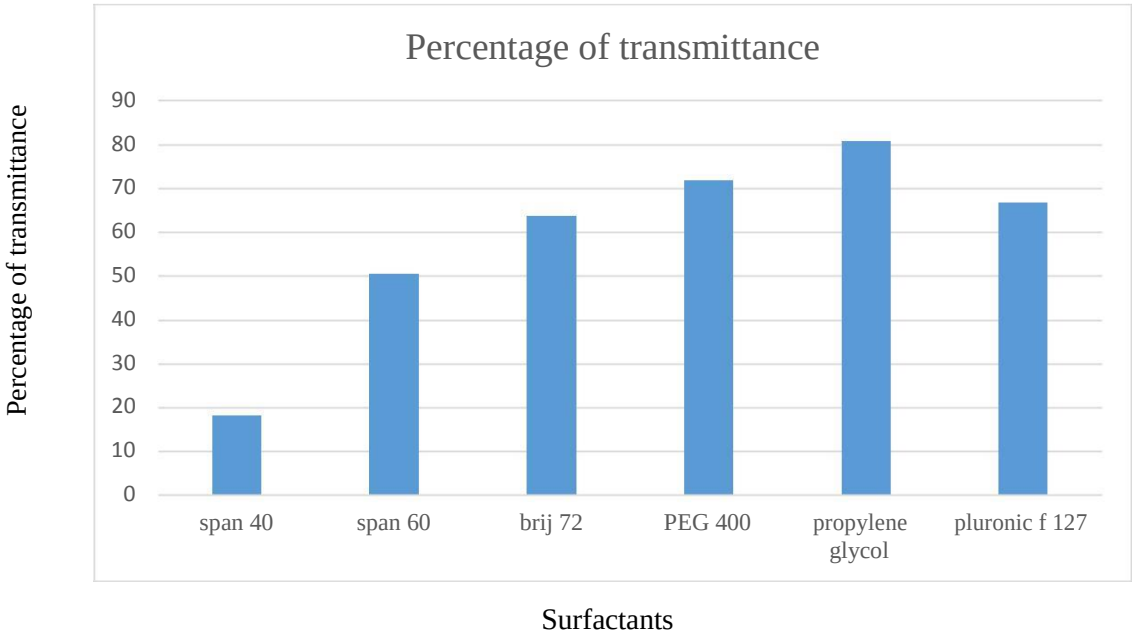
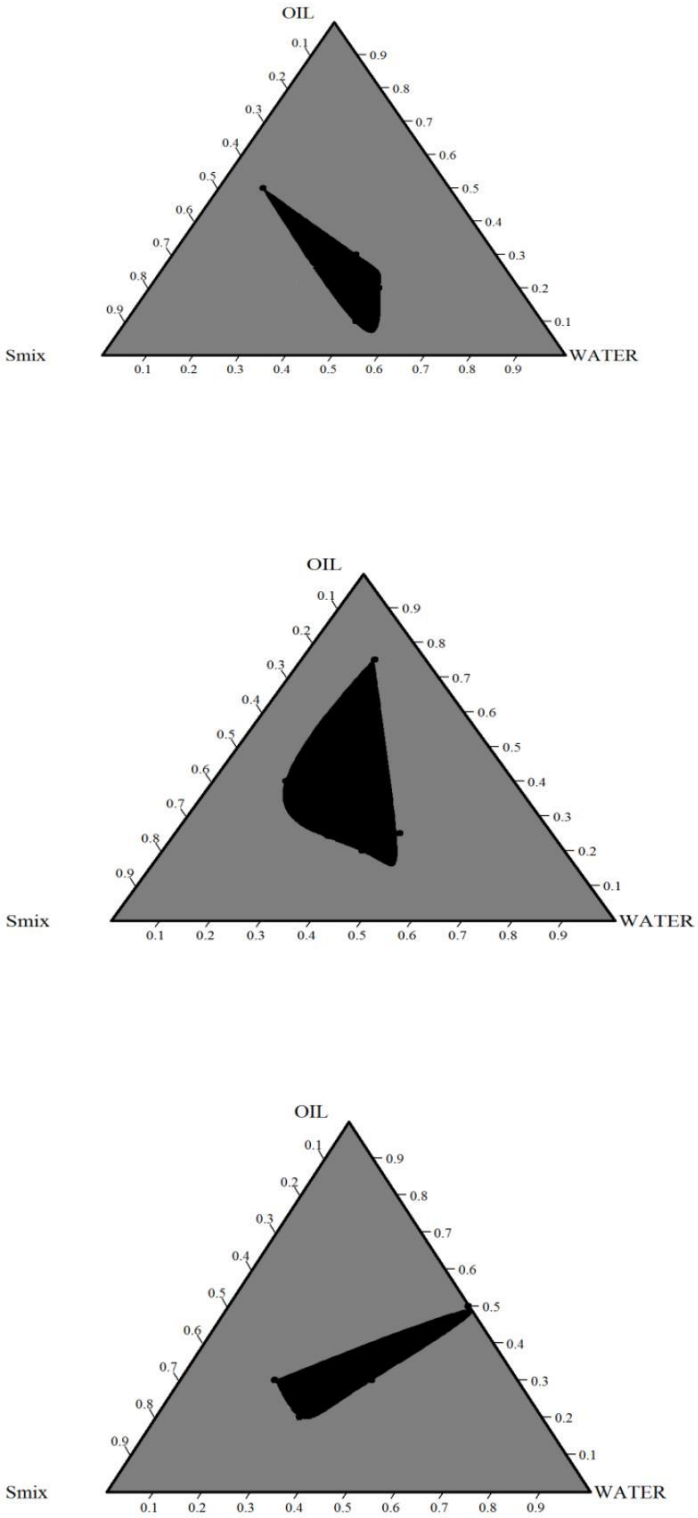


Figure 17: Percentage Transmittance of surfactants

Pseudoternary phase diagrams were constructed for identifying the self emulsifying regions.

It gives us an idea of the changes a SNEDDS under goes when diluted with gastric fluids Larger the shaded area in the diagram, more the self emulsification ability. From each phase diagram different concentrations of oil, at which nanoemulsions formed, were selected at a difference of 5% (10, 15, 20, 25 and 30) so that maximum formulations could be selected for optimizing the best formulation. Another phase diagram was also plotted without water to give us an idea of the miscibility of the other 3 excipients. Better self emulsification was seen with concentrations of surfactant above 50% and oil below 30%. Above these concentrations either phase separation or turbidity was seen.

Figure 18: Pseudo Ternary phase diagram



Evaluation

Visual assessment and self emulsification time

Formulations FT-11,FT-12,FT-13showed no phase separation or turbidity. Formulations with concentrations of oil below 30% and surfactant above 70% showed SNEDDS that have good clarity and No phase separation.

Visual assessment and self emulsification time

In nano-emulsion formulations only FT-11, FT-12and FT-13 were clear. The rest of the formulations showed precipitation.

Table 14: Visual assessment and self emulsification time of SNEDDS and S-SNEDDS formulations

Formulation	Visibility Grade	Precipitation
FT 1	III	Yes
FT 2	III	No
FT 3	III	Yes
FT 4	III	No
FT 5	III	Yes
FT 6	III	Yes
FT 7	III	Yes
FT 8	III	Yes
FT 9	III	No
FT 10	III	Yes
FT 11	III	No
FT 12	III	No
FT 13	III	No

Droplet size and Zeta potential

The size of droplets after nanoemulsification is the most important factor as it affects the absorption of the drug as well as drug release. The smaller droplets have larger surface area thereby increasing the absorption. The size of droplets decreased with high concentration of either oil or surfactant. PDI is the ratio of standard deviation to the mean droplet size. It indicates the uniformity of size range in the formulation. Zeta potential denotes the charge of repulsion among the particles. A high zeta potential for small particles is indicative of better stability. The particle size of FT11, FT12 &FT13 range from 277nm,246nm&220 nm with PDI from 0.159, 0.385&0.395

Table 15: Characterzation of S-SNEDDS formulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)
FT11	181	0.199	-0.118
FT12	273	0.201	-4.44
FT13	220	0.395	-6.49

Robustness to dilution

The formulations were diluted in various ratios to assess the performance of the S-SNEDDS in the body. The diluted S-SNEDDS showed no precipitation or phase separation indicating the stability of the nanoemulsions

Self emulsification time:

1ml of formulations was added to 100ml of distilled water at 37° C being agitated at 100rpm. The time required for the formation of a milky emulsion was noted for FT11, FT 12 &FT13 were 83secs,94secs &77secs

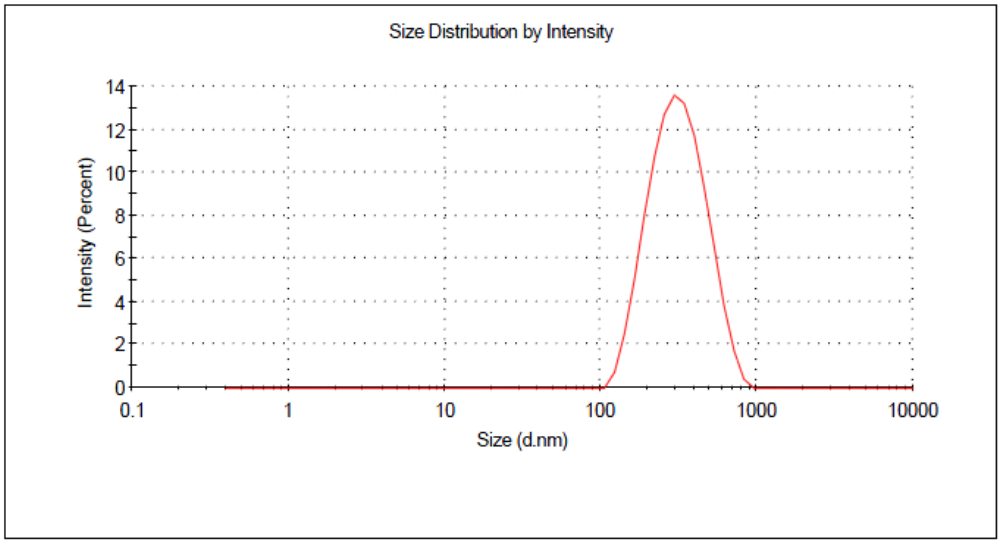
Particle size of FT11:

Figure 19: particle size of FT11

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 277.8	Peak 1:	332.5	100.0	133.2
PdI: 0.159	Peak 2:	0.000	0.0	0.000
Intercept: 0.681	Peak 3:	0.000	0.0	0.000

Result quality : Good



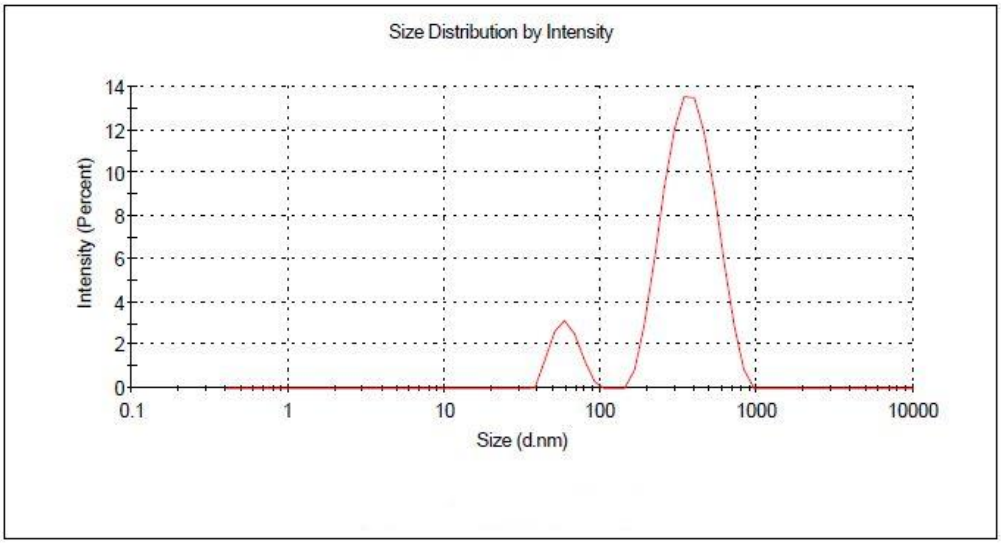
Particle size of FT12:

Figure 20: particle size of FT 12

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 246.7	Peak 1:	390.0	88.7	136.2
PdI: 0.385	Peak 2:	60.47	11.3	11.65
Intercept: 0.797	Peak 3:	0.000	0.0	0.000

Result quality : Good



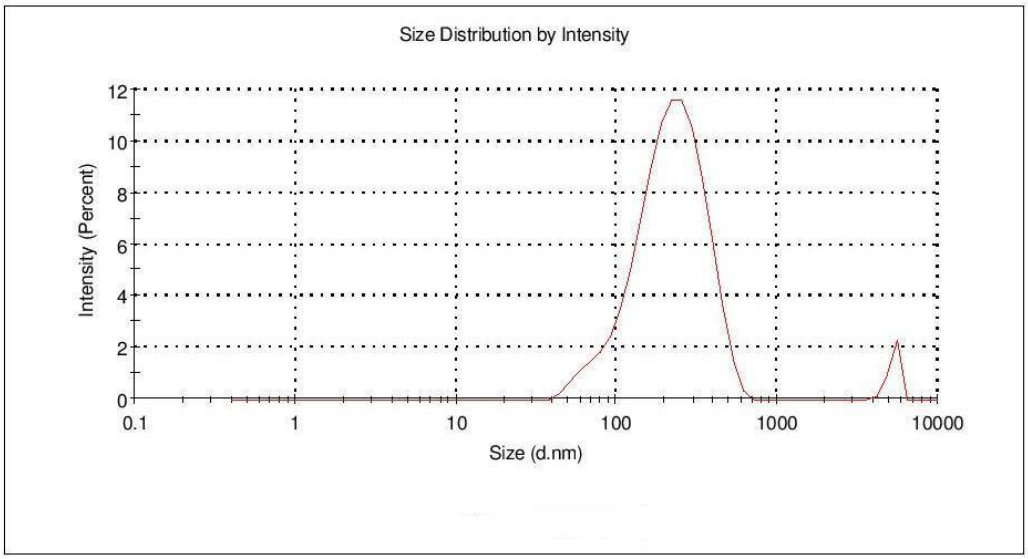
Particle size of FT13:

Figure 21: Particle size of FT13

Results

			Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	220.0	Peak 1:	234.3	96.7	107.4
PdI:	0.395	Peak 2:	5303	3.3	399.0
Intercept:	0.915	Peak 3:	0.000	0.0	0.000

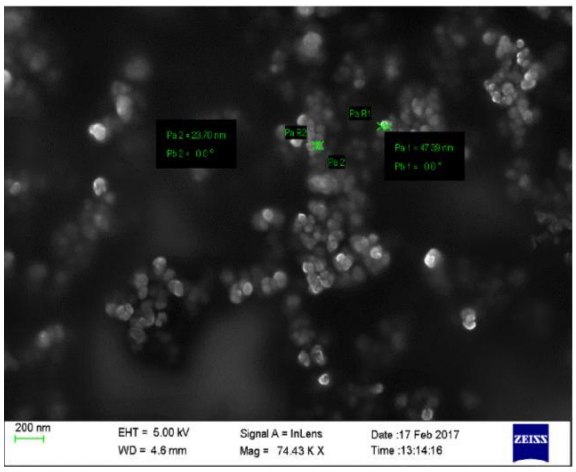
Result quality : Good



MORPHOLIGICAL STUDIES

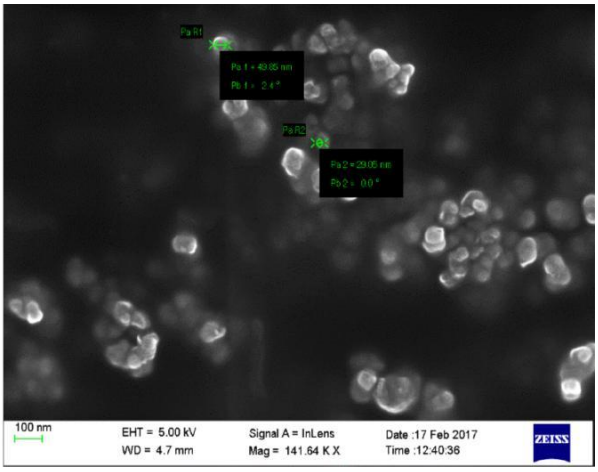
SCANNING ELECTRON MICROSCOPY

Figure 22:SEM image of FT11



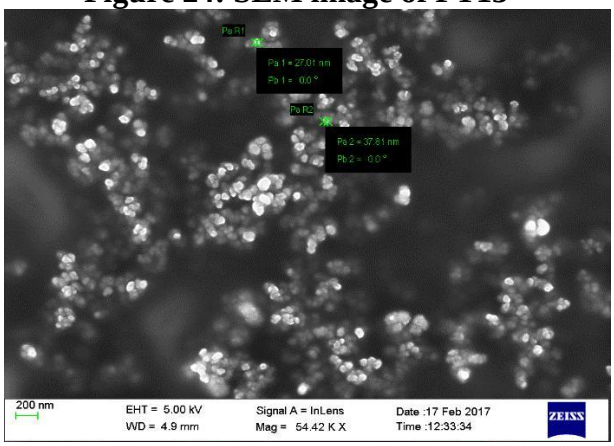
FT11

Figure 23:SEM image of FT12



FT12

Figure 24: SEM image of FT13



FT13

Conversion of liquid S-SNEDDS to solid form (SNE tablets)

FT11 , FT12and FT13 were mixed with avicel PH 101 in varying amounts from 50mg – 500 mg, yielded a free flowing powder that was further dried in the oven for 30 mins. For the tablet compression, the selected binders were Lactose and dicalcium phosphate. Tablets were punched with magnesium stearate and talc as lubricant.

DRUG CONTENT IN S-SNEDDS :

100mg of nanoformulation was dissolved in 100ml of distilled water.From this 1ml was taken and made upto 10ml.further from this 1ml was taken and made upto 10ml and absorbance was taken at 294nm using UV-spectrophotometer. From this the required amount of nano formulation to be made into tablet and it is being calculated.

Characterization of telmisartan S-SNEDDS:

Micromeritic properties of S-SNEDDS:

The values obtained for the angle of repose of the three formulae FT11,FT12 and FT13 after adding glidant were 32˚Ɵ,33˚Ɵ and 35˚Ɵ.these values indicate that all formulae have good flowability .the bulk density of the thee formulae FT11,FT12 and FT13 was found to be 0.29g/ml,0.27g/ml and 0.24g/ml respectively.however,tapped density was 0.32g/ml,0.33g/ml and 0.37g/ml.Carr's index of formulae FT11,FT12 and FT13 was found to be 9.37,15 and 9 respectively which give an indication about the good flowability of the three S-SNEDDS formulae.this was further supported by the values of Hausner's ratio.the results of Hausner's ratio of formulae FT11,FT12 and FT13 were 1.09,1.18 and 1.1 respectively. the improved flowability of S-SNEDDS formulae may be due to good sphericity of particles these three formulae goes for tablet compression.

Table 16: Micromeritics properties of SNE powder formulation

Before adding glidant

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Angle of repose(Ɵ)
FT11	0.22	0.35	34	1.5	45
FT 12	0.23	0.33	30	1.4	45
FT13	0.24	0.34	28	1.4	46

Table 17: Micromeritics properties of SNE powder formulation

After adding Talc 2%

Formulation code	Bulk Density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Ɵ)
FT11	0.29	0.32	9.3	1.09	32
FT12	0.27	0.33	15	1.18	33
FT13	0.24	0.37	9	1.1	35

COMPRESSION OF TELMISARTAN SNE TABLET:

Table 18: Compression of telmisartan SNE tablet

PUNCHING OF TELMISARTAN SNE – TABLET (FT 11)	**Telmisartan 20mg** (excipients- dicalcium phosphate/ lactose / micro crystalline cellulose/magnesium stearate & talc	**For 1 tablet:** Drug – 20 mg Excipients- 113mg/100mg/190mg Magnesium stearate 2% Talc 1%
PUNCHING OF TELMISARTAN SNE – TABLET (FT 12)	**Telmisartan 20mg** (excipients- dicalcium phosphate/ lactose / micro crystalline cellulose /magnesium stearate & talc	**For 1 tablet:** Drug – 20 mg Excipients- 102mg/110mg/170mg Magnesium stearate 2% Talc 1%
PUNCHING OF TELMISARTAN SNE – TABLET (FT 13)	**Telmisartan 20mg** (excipients- dicalcium phosphate/ lactose /micro crystalline cellulose /magnesium stearate & talc	**For 1 tablet:** Drug – 20 mg Excipients- 123mg/100mg/190mg Magnesium stearate 2% Talc 1%
Formulation FT11 contains 87mg of telmisartan nanoformulation equivalent to 20mg of telmisartan pure drug (with excipients)	**Formulation FT12 contains 118mg of telmisartan nanoformulation equivalent to 20mg of telmisartan pure drug (with excipients)**	**Formulation FT13 contains 77mg of telmisartan nanoformulation equivalent to 20mg of telmisartan pure drug (with excipients)**

FT11 Telmisartan SNE tablets

Figure 25: FT11 Telmisartan SNE tablets

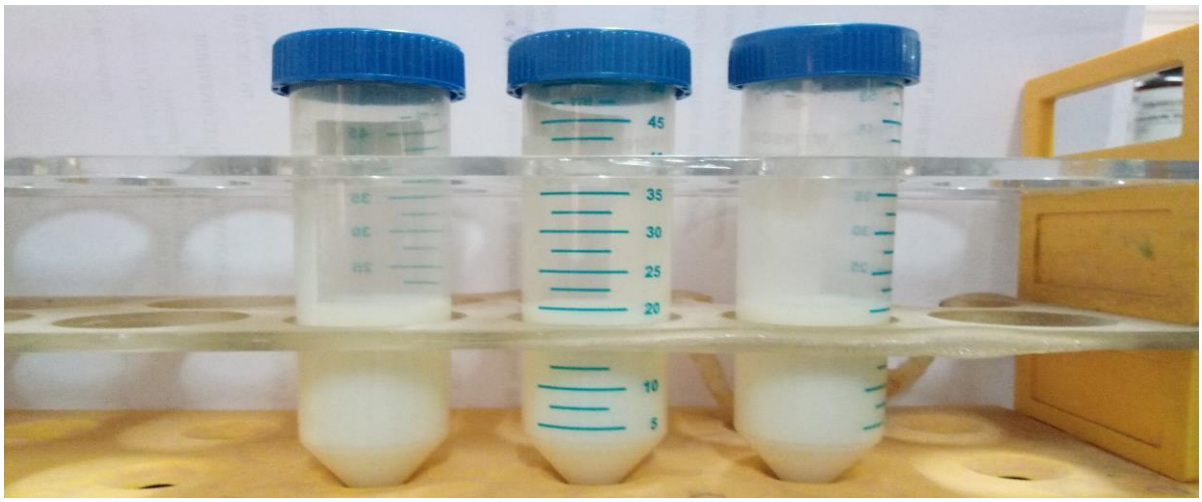
FT12 Telmisartan SNE tablets

Figure 26: FT12 Telmisartan SNE tablets

FT13 Telmisartan SNE tablets

Figure 27: FT13 Telmisartan SNE tablets

Figure 28: Formulation of Telmisartan Liquid SNEDDS



Evaluation of Telmisartan SNE tablet:

Weight variation test:

Table 19: Weight variation test

Formulation code	Weight variation (%)
FT11	3.8
FT12	4.4
FT13	4.5

The percentage weight variation for all formulations was performed. All the formulations passed weight variation test as per the pharmacopeial limits of 5% as shown in the table above

Friability test:

Table 20: Friability test

Formulation code	Friability (%)
FT11	0.28
FT12	0.24
FT13	0.26

The friability test for formulations was performed. All the formulations passed friability test as per the pharmacopeial limits as shown in the table.

Hardness test:

Table 21: Hardness test

Formulation code	Hardness (Kg/cm^2)
FT11	5
FT12	4
FT13	5

The hardness of formulations was carried out and found that it was 4 to 5 Kg/cm^2 for formulations FT11, FT12 and FT13 are passed and within this limits as shown in the table above.

Disintegration test:

Table 22: Disintegration test

Formulation code	Disintegration time (mins)
FT11	4
FT12	4
FT13	6

The disintegration test for all formulation was performed. All the formulations passed disintegration test as per the pharmacopeial limits as shown in the table.

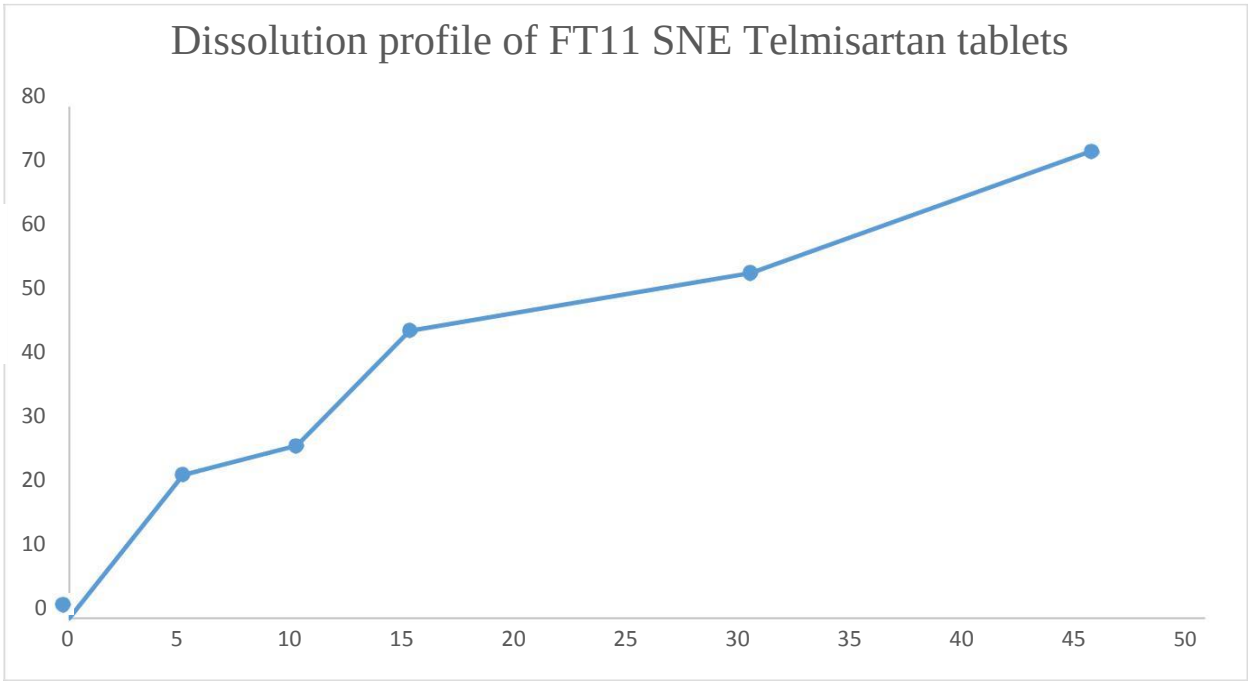
Dissolution study

Dissolution data of FT11 Telmisartan SNE tablet

Table 23: Dissolution data of FT11 telmisartan SNE tablet

Time (minutes)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release (mg)	Percentage of drug release (%)
5	0.66	0.5	4.5	22.5
10	0.79	0.6	5.4	27
15	0.134	1	9	45
30	0.162	1.2	10.8	54
45	0.182	1.4	12.6	73

Figure 29: Dissolution profile of FT11 SNE Telmisartan tablet

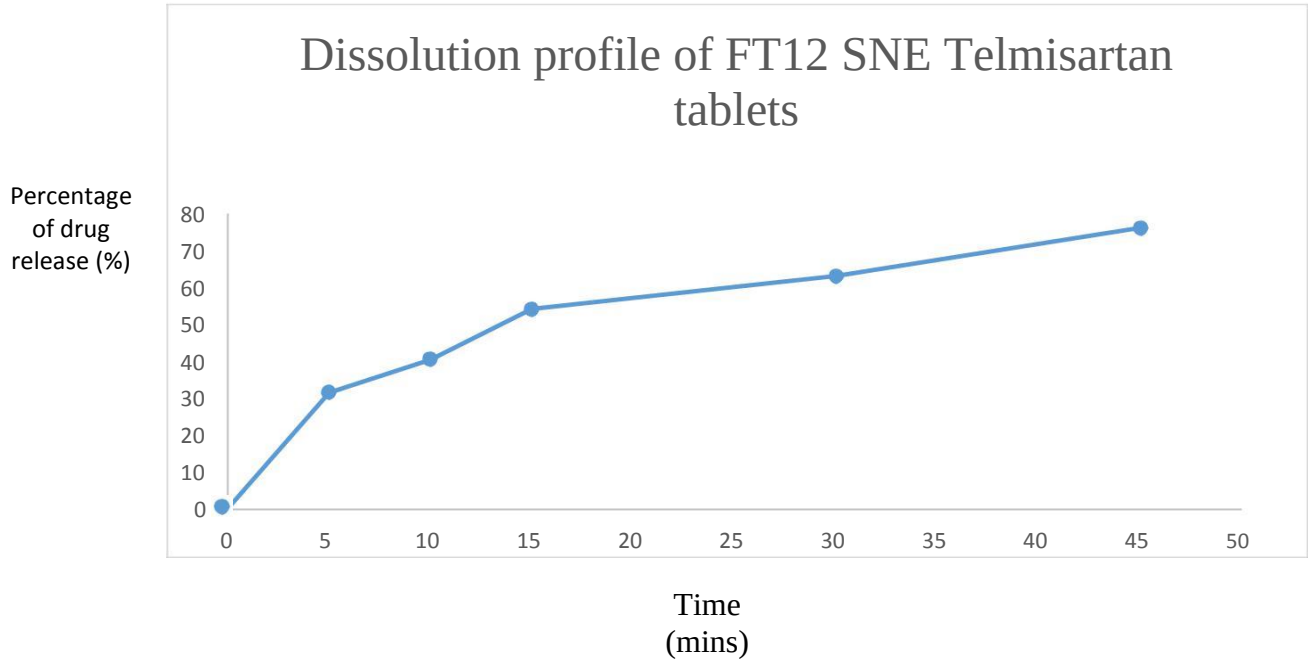


Dissolution data of FT12 Telmisartan SNE tablet

Table 24: Dissolution data of FT12 Telmisartan SNE tablets

Time (minutes)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release (mg)	Percentage of drug release (%)
5	0.93	0.7	6.3	31.5
10	0.107	0.9	8.1	40.5
15	0.159	1.2	10.8	54
30	0.184	1.4	12.6	63
45	0.257	1.6	14.4	76

Figure 30: Dissolution study of FT12 SNE Telmisartan tablets

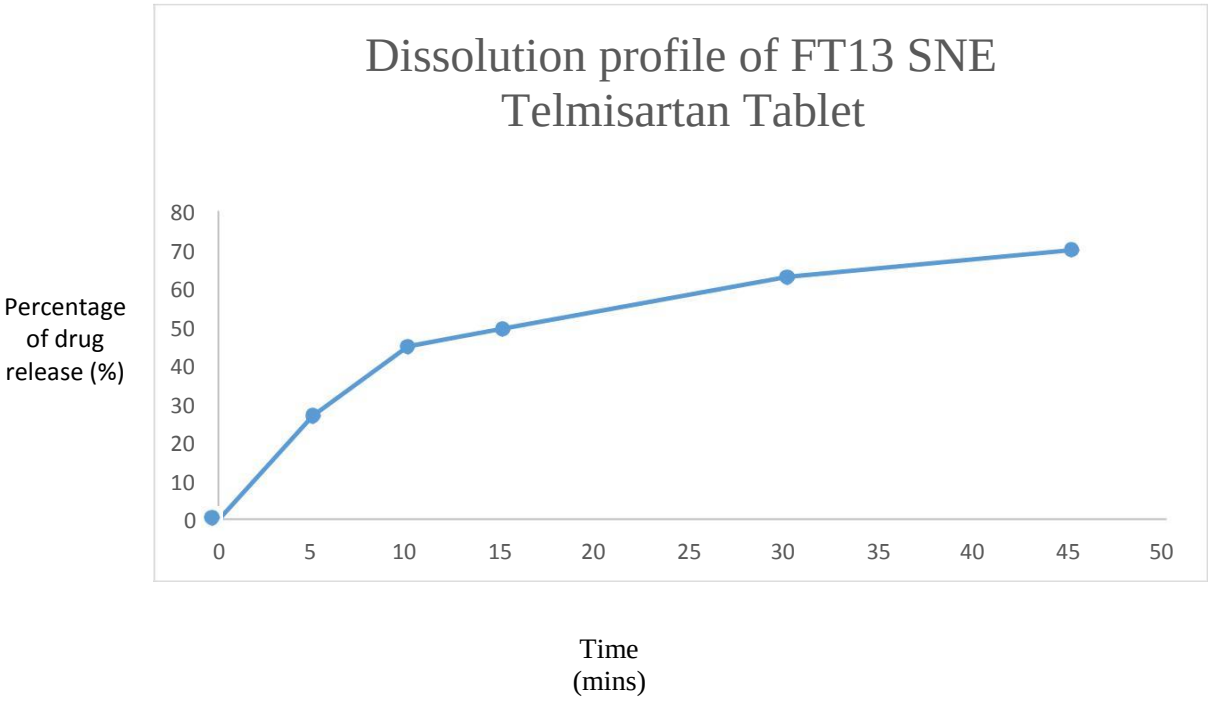


Dissolution data of FT13 Telmisartan SNE tablet

Table 25: Dissolution data of FT13 Telmisartan SNE tablet

Time (minutes)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release(mg)	Percentage of drug release (%)
5	0.070	0.6	5.4	27
10	0.128	1	9	45
15	0.133	1.1	9.9	49.5
30	0.164	1.4	12.6	63
45	0.211	1.6	14.4	72

Figure 31: Dissolution profile of FT13 SNE Telmisartan tablets

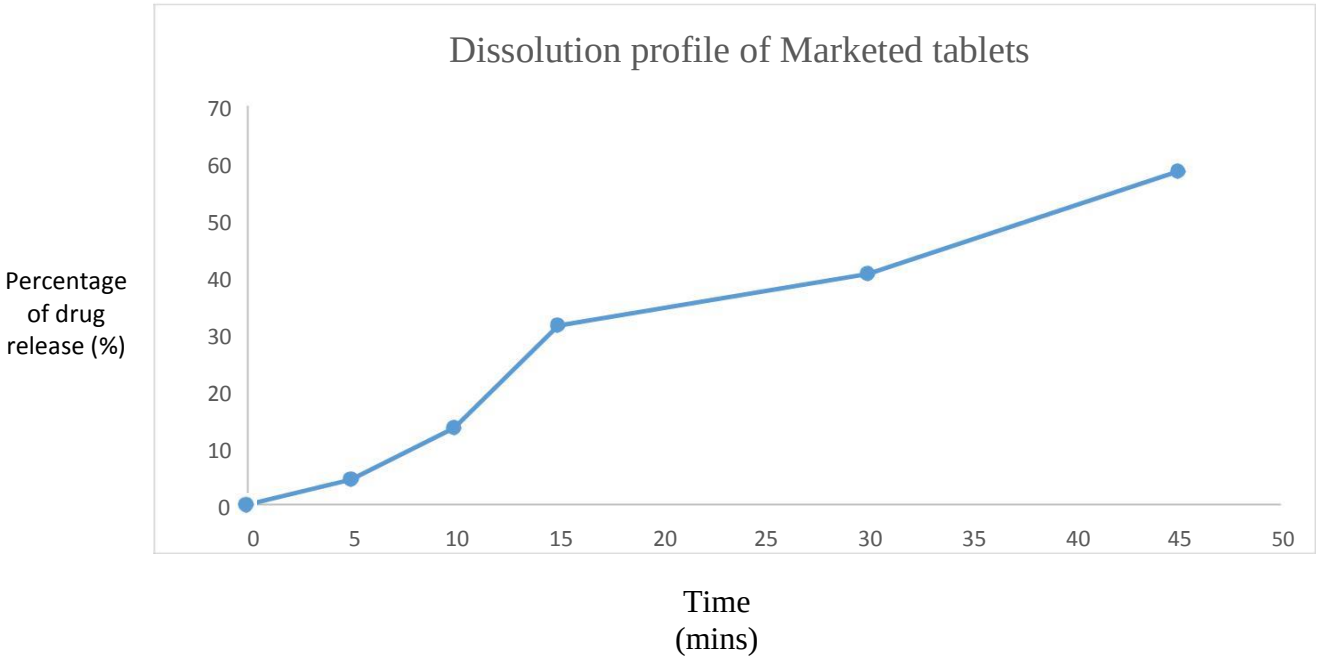


Dissolution data of Telmisartan tablet- market formulation

Table 26: Dissolution data of Telmisartan tablet- marketed formulation

Time (minutes)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release(mg)	Percentage of drug release (%)
5	0.022	0.1	0.9	4.5
10	0.049	0.3	2.7	13.5
15	0.098	0.7	6.3	31
30	0.110	0.9	8.1	40.5
45	0.174	1..3	11.7	58.5

Figure 32: Dissolution profile of Telmisartan marketed tablets



SUMMARY AND CONCLUSION

Oral route is the most convenient route of administration but it faces the problem of low oral bioavailability. Self nano emulsifying therapeutic system (SNETS) can be used to overcome the problems faced while using low aqueous soluble drugs. These systems form emulsion *in situ* with have good stability. This study aimed at investigating the increase in the bioavailability by administering a BCS class II drug, in a SNEDDS form and was compared to the conventional telmisartan tablets.

It can be concluded from the experimental study carried out that the formulation of a poorly water soluble drug, telmisartan into Self Nanoemulsifying Drug Delivery System yields a formulation with nano size range & good zeta potential. The liquid was further made into tablet form for better stability. The prepared formulations were characterized for the size, zeta potential, self-emulsification time and drug content & compressed into tablets.

The *in vitro* study of the best formulation FT12 SNE tablet showed 1.4 fold increase in the bioavailability when compared to the marketed formulation.